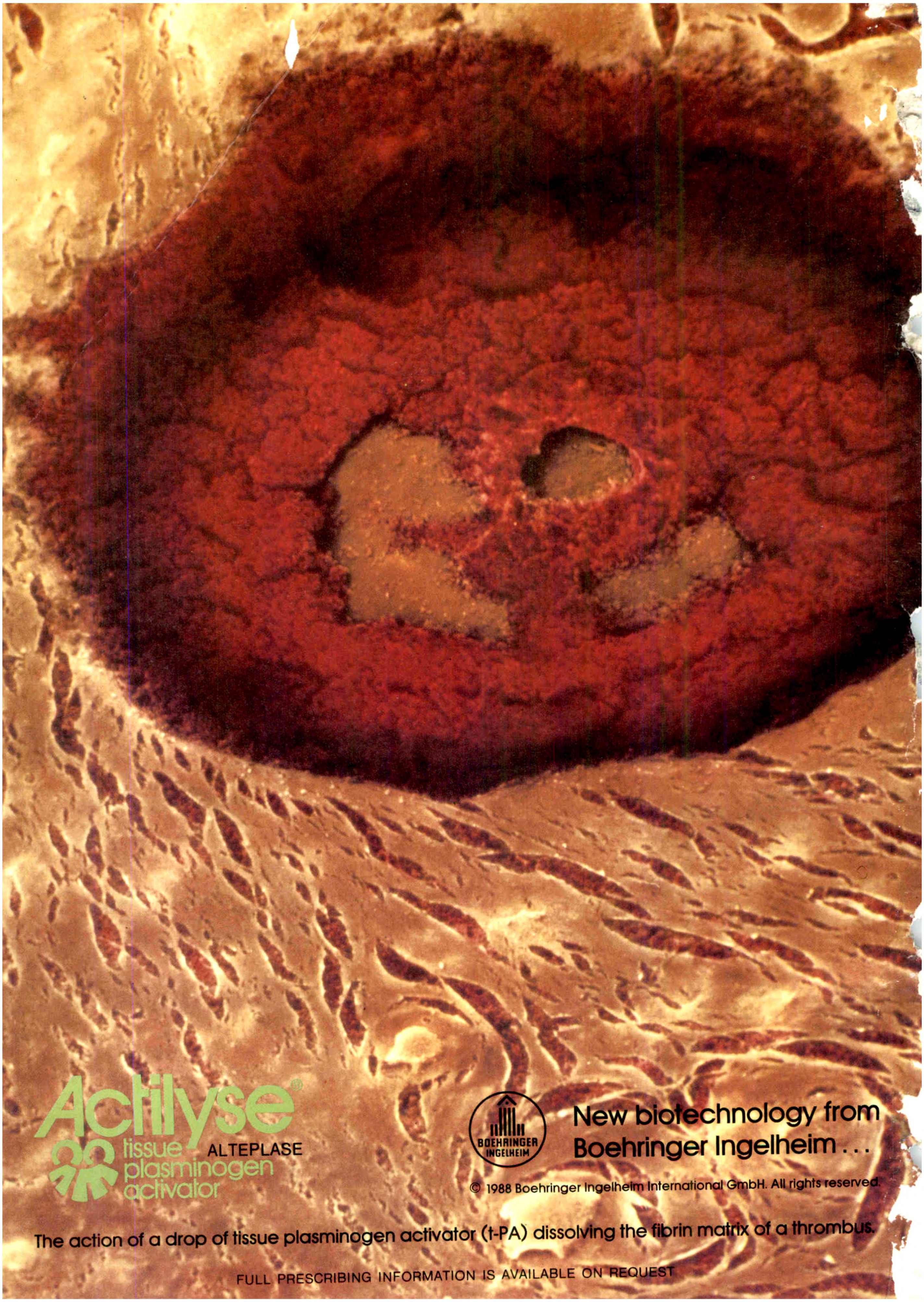

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The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is typeset and printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal*, established in 1980.

The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers, written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

The *Annals* publishes original articles, case reports, letters to the editor, editorials, and from time to time, special communications, commentaries, and review articles. Abstracts of meetings and symposia sponsored by the Joint Board for Postgraduate Medical Education of Saudi Arabia are published, and the proceedings of such symposia may be published if the Editorial Board considers them appropriate and relevant. The Editorial Board wishes to minimize delay between manuscript submission, decision, and publication, and accordingly authors are requested to follow carefully the instructions set out under "Information for Authors."

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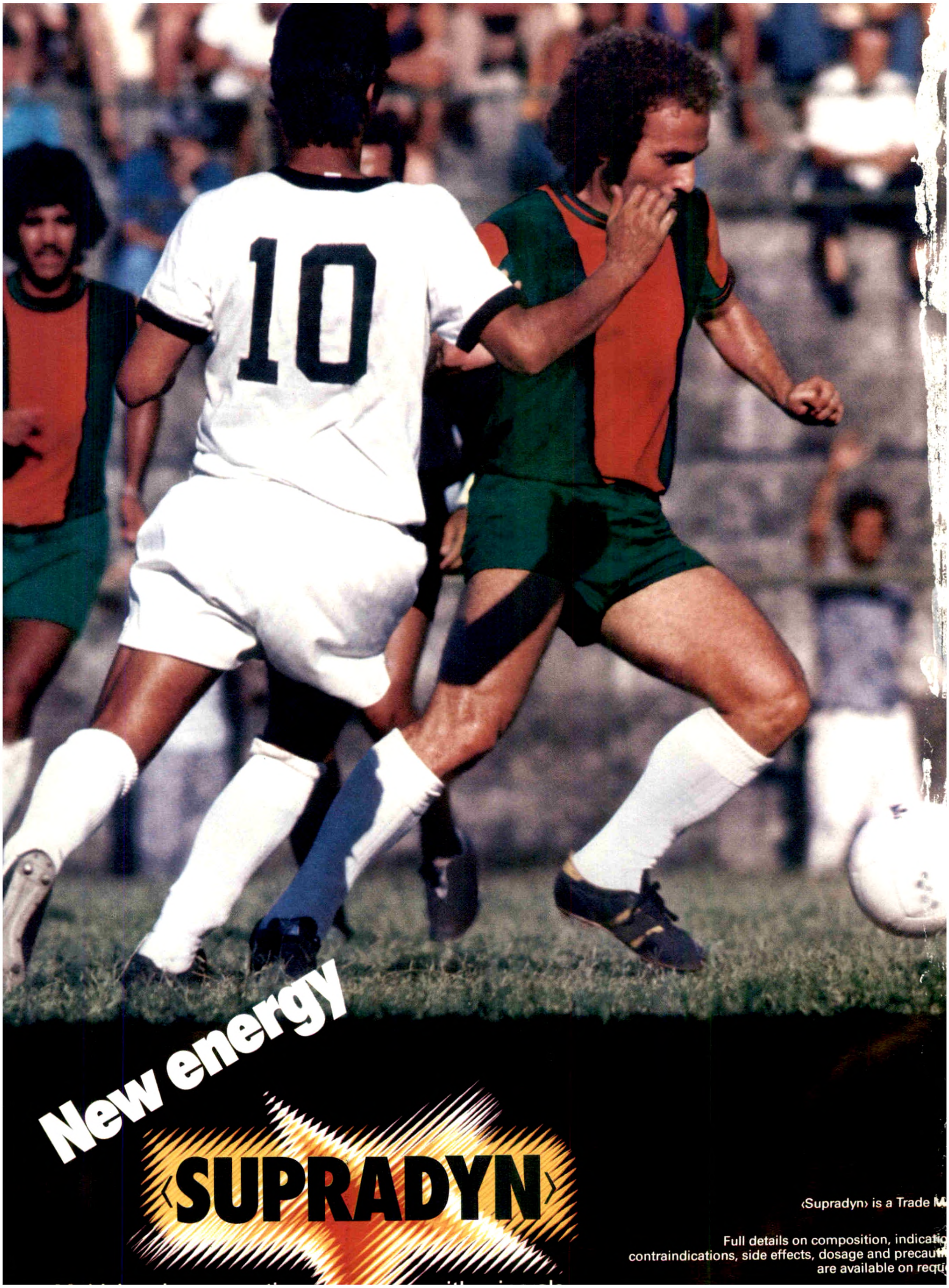

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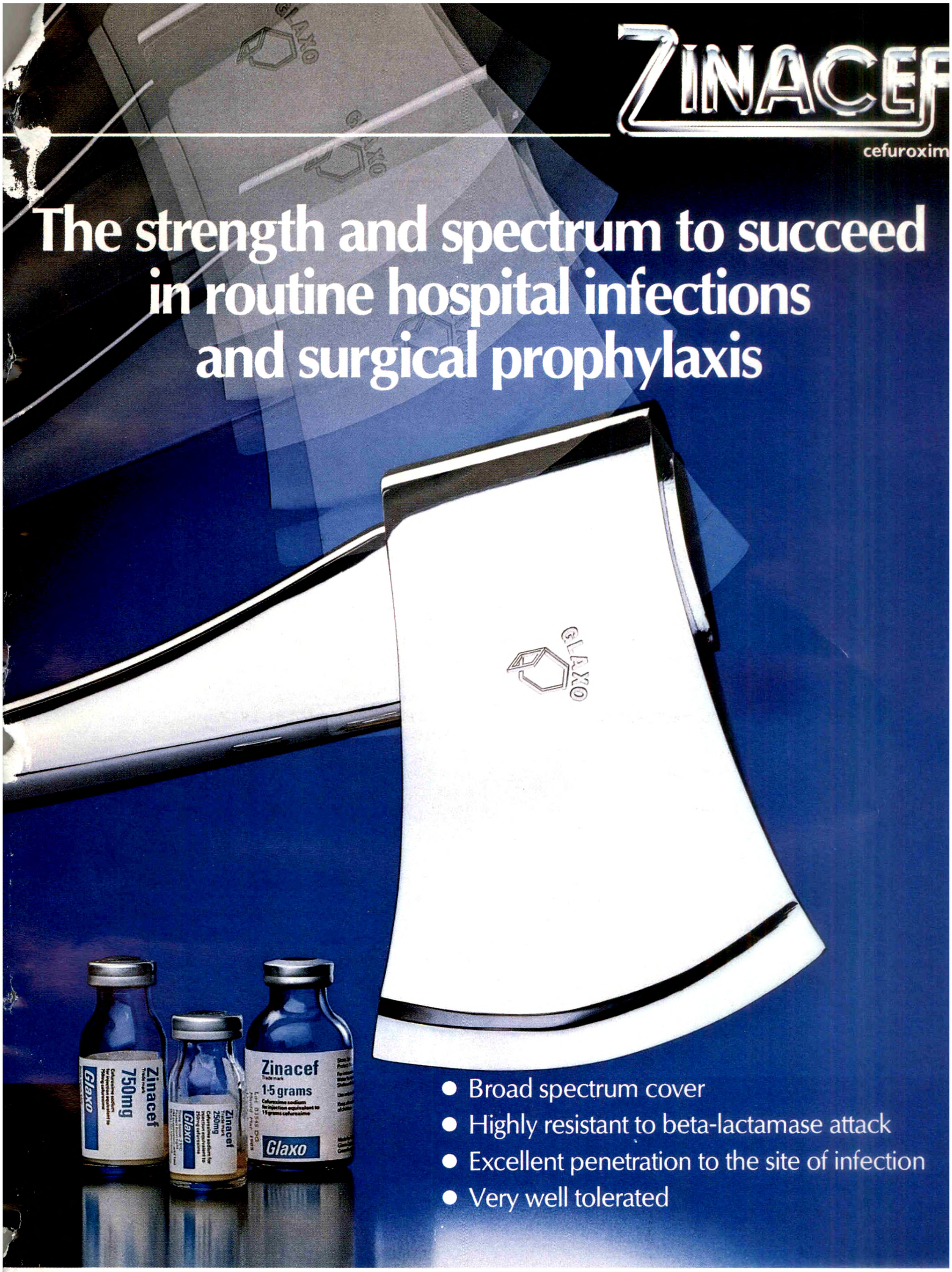

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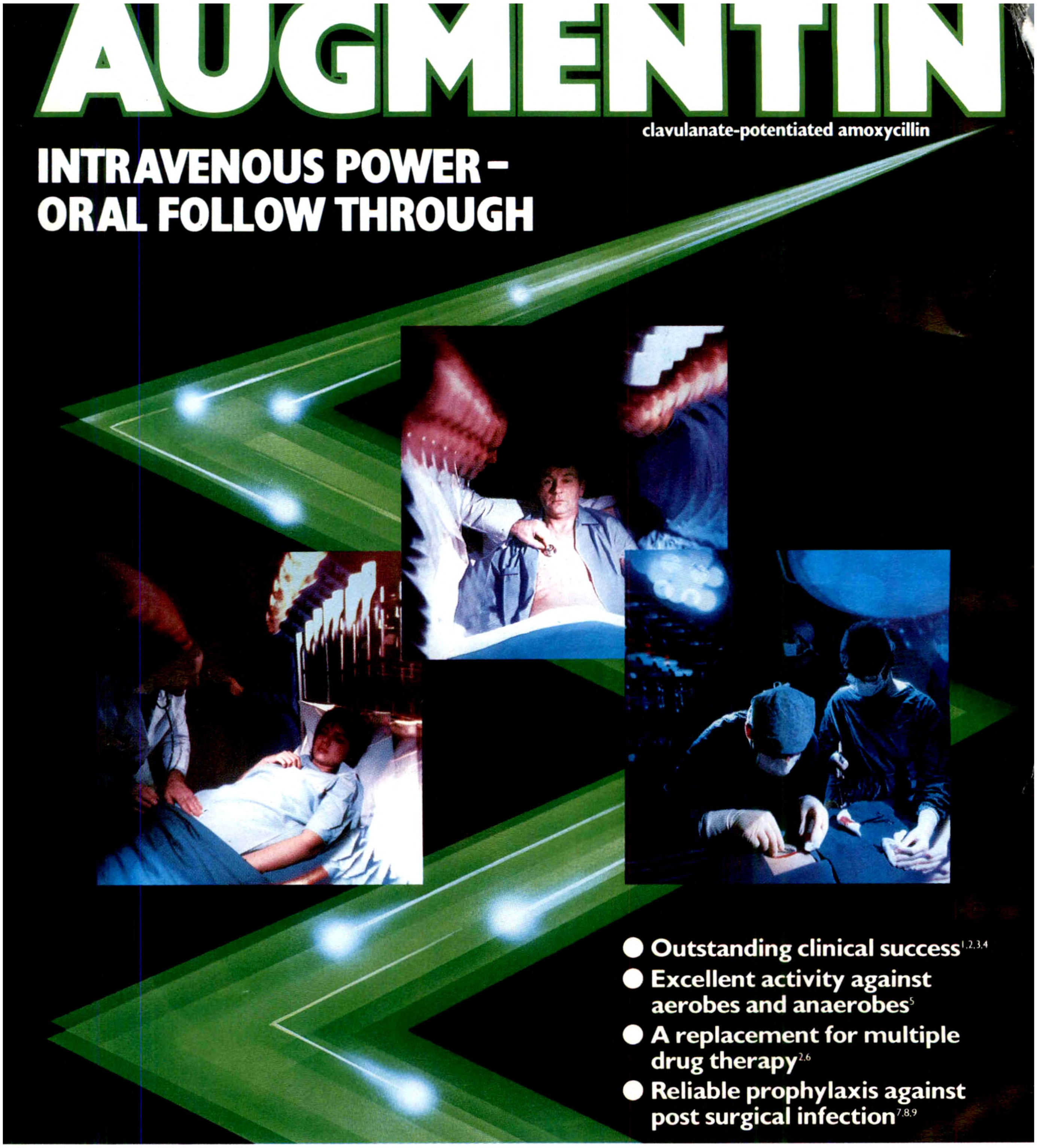

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References 1. Excerpta Medica, **CCP4**, (1983), 207. 2. J. Antimicrob. Chemother., (1982) **10**, (1), 67. 3. Proc. 4th Mediterr. Congr. Chemother. Rhodes, (1985), **4**, (2 suppl.): 199. 4. Excerpta Medica, **ICS 544**, (1980), 277. 5. Ibid. (1980), 173. 6. Med. Int. (1983), (Suppl: Readings in Infections), 2. 7. Proc. 4th Mediterr. Congr. Chemother. Rhodes, (1985), **4**, (2 Suppl.), 776. 8. Br. J. Surg., (1985), **72**, (7), 571. 9. Proc. 26th ICAAC New Orleans, (1986), Abstr. 472.

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IMPORTANT NOTICE The World Health Organisation (WHO*) has recommended that pregnant women and new mothers be informed of the benefits and superiority of breastfeeding – in particular the fact that it provides the best nutrition and protection from illness for babies.

Mothers should be given guidance on the preparation for, and maintenance of, lactation, with special emphasis on the importance of a well-balanced diet both during pregnancy and after delivery. Unnecessary introduction of partial bottle-feeding or other foods and drinks should be discouraged since it will have a negative effect on breastfeeding. Similarly, mothers should be warned of the difficulty of reversing a decision not to breast-feed.

Before advising a mother to use an infant formula, she should be advised of the social and financial implications of her decision: for example, if a baby is exclusively bottle-fed, more than one can (450 g) per week will be needed, so the family circumstances and costs should be kept in mind. Mothers should be reminded that breast-milk is not only the best, but also the most economical food for babies.

If a decision to use an infant formula is taken, it is important to give instruction on correct preparation methods, emphasizing that unboiled water, unboiled bottles or incorrect dilution can all lead to illness.

* See: International Code of Marketing of Breast Milk Substitutes, adopted by the World Health Assembly in Resolution WHA 34.22, May 1981.

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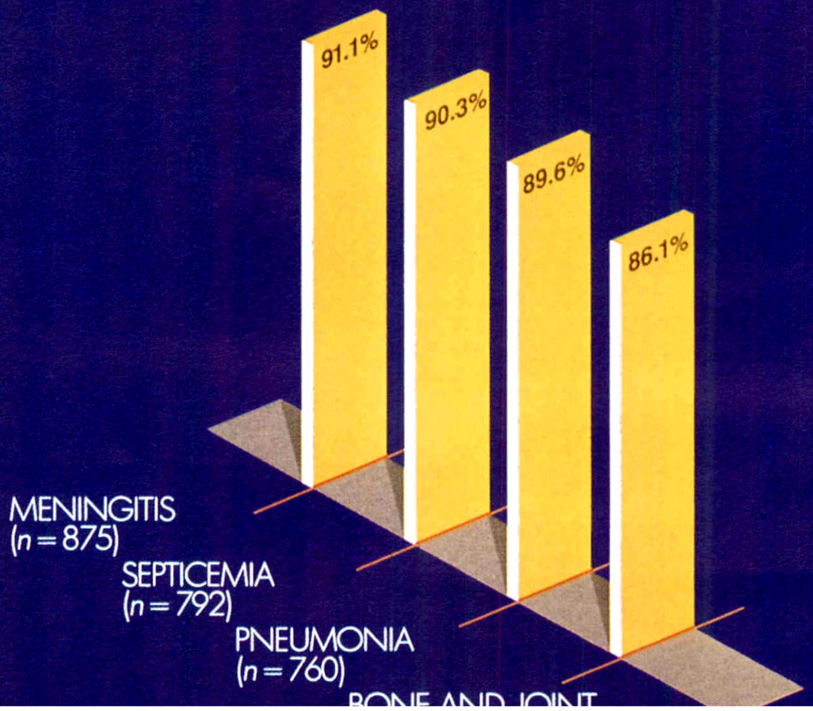

Editorial

ETHICS IN CLINICAL RESEARCH

Informed consent - In order to protect the safety and dignity of human subjects in experimental investigations, academic institutions and grant-giving agencies have in recent years come to require that the nature and purpose of all procedures, and their attendant possible risks, be fully explained to potential subjects in advance.

In days gone by, it was accepted in many communities around the world that doctors knew what was best for their patients, and that by and large it was inappropriate for patients to question their doctors. But such God-like attitudes on the part of the medical profession, and such unquestioning obedience on the part of patients, are no longer acceptable. Many factors over the past few decades have contributed to the need for appropriate information being given to the patient, so that he or she can make or contribute to informed decisions, particularly relating to drug treatment, surgical procedures, and invasive investigations.

This necessary dialogue has come to be applied to clinical research. Perhaps the greatest impetus to the recognition of the need for strict guidelines limiting research on human beings came from the atrocities committed in the name of medical research in concentration camps during the Second World War. Realization of these appalling experiments led to the promulgation of the Nuremberg Code in 1947 and the World Medical Association Declaration of Helsinki, revised in 1975.[1] Both the Nuremberg Code and the Declaration of Helsinki bluntly require voluntary, informed consent by the human subject in any medical experiment on human beings. The Declaration of Helsinki includes the statement that "concern for the interests of the subject must always prevail over the interest of science and society."

Recently, there has been some thought-provoking discussion in the *New England Journal of Medicine* concerning the ethics of medical research in developing countries.[2,3] The special problems associated with clinical research on the acquired immunodeficiency syndrome (AIDS) in Africa highlight some interesting points. One author[3] states that "the basic ethical principles that guide human investigation, as defined by the Helsinki Declaration and Nuremberg Code, need to be interpreted and applied within cultural settings, many of which were unfamiliar to the international bodies that originally formulated these principles. The basic bioethical principles may have very different meanings in such settings; foreign investigators need to be sensitive to these different perspectives before conducting studies." This surely is begging the question—whatever local customs or practices there may be, the basic proposition remains that no human research should be undertaken without informed consent. Thus, for example, language barriers are no excuse or reason not to arrange for informed consent. And tribal or ethnic customs whereby the permission of the village chief or the husband must first be obtained do not relate to the basic ethics of informed consent, but only the *modus operandi* of undertaking the work at all!

In an editorial,[2] the vital question is posed "whether official standards are relative, to be weighed against competing claims and modified accordingly, or whether, like scientific standards, they are absolute."

Extraordinarily, it has been suggested[2] that to insist on certain ethical standards when doing research in another country is a form of imperialism and therefore inappropriate. Such woolly thinking is not an argument for tolerance, but a travesty of justice for all. The right of self-determination, on which the doctrine of informed consent is based, surely is fundamental and should not be tinkered with in any society.

Such a firm line of sticking to ethical principles does not affect the obvious need for Western or other researchers to respect local sensitivities. An important example may be the necessity to obtain permission from a husband before approaching his wife to enroll her in a clinical study. Yet obtaining *his* permission does not absolve the researcher from gaining the *wife's informed* consent.

In many countries, there are well established human ethics committees or institutional review boards whose task it is to review clinical research protocols to ensure that they conform to ethical standards. These boards usually are based on university schools of medicine or on hospitals. Such committees exist in many institutions here in the Middle East, and it is strongly recommended that where they do not, they should be established.

The *Annals of Saudi Medicine* has always presumed that manuscripts involving clinical research on human subjects have followed an ethical protocol. Henceforth, as noted in the amplified "Information for Authors," we will require that such papers include a statement confirming that the human investigations were performed after approval by a local human ethics committee and that appropriate informed consent was obtained from each subject or subject's guardian.

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References

1. Cited in Beauchamp TL, Childress JF, eds. Principles of biomedical ethics. 2nd ed. Oxford: Oxford University Press, 1983:338-43.
2. Angell M. Ethical imperialism: ethics in international collaborative clinical research. New Engl J Med 1988;319(16):1081-3.
3. Barry M. Ethical considerations of human investigation in developing countries: the AIDS dilemma. New Engl J Med 1988;319(16):1083-6.

Original Articles

ROAD TRAFFIC ACCIDENT FATALITIES IN RIYADH CENTRAL HOSPITAL 1400-1407H (1980-1987)

Qasim O. Al-Qasabi, FRCS; Mohammed A. Al-Mofarreh, FAMED;
AbdulRahman Al-Bunyan, FRCS; Abdullah A. Al-Kraida, FRCS;
Mohammed M. Haque, FRCS

زادت معدلات الاصابات الرضحية الناجمة عن الحوادث المرورية في الرياض بنسب معادلة للزيادة الكبيرة التي طرأت على أعداد السيارات. هذه الدراسة هي تحليل مراجعة عن الحوادث المرورية القاتلة التي وردت إلى مستشفى الرياض المركزي خلال ثمان سنوات. ورد إلى مستشفى الرياض المركزي خلال تلك الفترة ما مجموعه ٦٤٩٤٢ مصاباً اصيبوا في حوادث مرورية. زادت معدلات ضحايا الحوادث المرورية الذين يراجعون مستشفى الرياض المركزي تدريجيا في حين أن معدلات الوفيات كانت تتناقص على نحو ملحوظ، مما يدل على التطور الذي طرأ في العناية بضحايا الحوادث المرورية، سواء كان ذلك قبل وصولهم للمستشفى أو خلال فترة وجودهم فيه. تعتبر الحوادث المرورية السبب الرئيسي للوفيات في مستشفى الرياض المركزي لمختلف الأعمار وخصوصا للطاقات الشابة المنتجة الذين تقل أعمارهم عن ٤٠ عاما.

Trauma due to road traffic accidents (RTAs) in Riyadh has increased in direct proportion to the increasing number of cars. This study is an 8-year retrospective analysis of RTA fatalities at Riyadh Central Hospital (RCH). During this 8 years, 64,942 RTA victims attended RCH. Total RTA victims seen at RCH increased gradually with a steady decline in the number of deaths, which indicates improvement in care of RTA victims, both prior to arrival at the hospital and during hospitalization. At RCH, RTA is the primary cause of death for all age groups and especially for productive young adults below the age of 40 years.

Trauma due to road traffic accidents (RTAs) remains a major health problem, particularly as it affects mainly young citizens. This study is an 8-year (1400-1407H/1980-1987) retrospective analysis of RTA victims at Riyadh Central Hospital (RCH). The aim of this study was to evaluate care of RTA victims both before and during hospitalization over the last 8 years and to compare RTA as a cause of death with other major health problems encountered at RCH.

Materials and Methods

Riyadh Central Hospital is a 1150-bed general hospital which receives all brought-in-dead RTA victims of Riyadh City and most RTA injuries needing medical treatment. Riyadh City has a population of approximately 1.5 million persons.

Data concerning the total number of RTA patients seen at RCH were analyzed. All the RTA victims admitted to the hospital or treated in the emergency room were recorded, as well as the total number of brought-in-dead victims.

Hospital death was defined as death occurring within 30 days of RTA injury.[1] The major causes of hospital death in different age groups were also analyzed in relation to RTA fatality and compared to the figures from the United States.[2-4] The relationship of the growing number of cars to the

---

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Accepted for publication 25 July 1988.

increasing number of RTAs was also noted.

Results

Over 214,000 patients were admitted to RCH in the 8-year study period, and 10.87% of these were RTA victims (Table 1). Of the 64,942 RTA victims seen at RCH, 41,610 (64.1%) were discharged from the emergency room on an ambulatory basis after satisfactory medical treatment. The remaining 23,332 RTA victims were admitted to RCH with various grades of trauma.

The total number of RTA victims seen at RCH gradually increased during the 8-year study period, though the number of hospital deaths steadily diminished from 277 in 1400H to 126 in 1407H (Table 2), and the number of brought-in-dead victims declined from 392 in 1400H to 268 in 1407H (Figure 1). The hospital mortality and brought-in-dead figures have been compared for the 8-year period in Figure 2.

The average RTA hospital mortality for the 8-year study period (death after admission) was 2.56% (Table 2), and the overall RTA mortality (both before arriving at the hospital and during hospitalization) for the same period was 6.91%

TABLE 1. *RTA admissions as % of admissions.*

Year	Admissions Total	No. (%) due to RTAs
1400	19,769	2876(14.55)
1401	21,008	2663(12.68)
1402	24,794	3218(12.98)
1403	26,841	3694(13.76)
1404	32,762	3305(10.09)
1405	29,534	2875(9.73)
1406	29,583	2431(8.22)
1407	30,310	2270(7.49)
Total	214,601	23,332(10.87)

TABLE 2. *RTA hospital mortality.*

Year	No. of RTA victims seen at RCH	No. (%) of RTA deaths after admission
1400	6800	277(4.07)
1401	7210	248(3.43)
1402	8890	259(2.91)
1403	9212	235(2.55)
1404	8608	194(2.25)
1405	7758	182(2.34)
1406	8211	143(1.74)
1407	8253	126(1.53)
Total	64,942	1664(2.56)

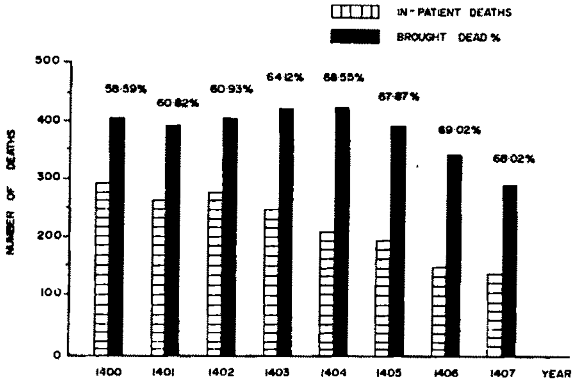

FIGURE 1. RTAs at RCH, 1400-1407H.

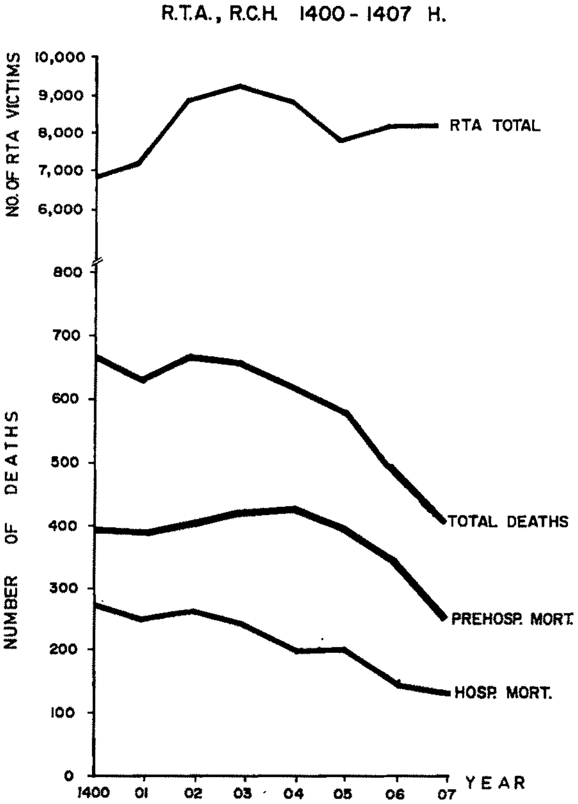

FIGURE 2. Relationship between inpatient deaths and brought-in-dead victims of RTAs. The percentage indicates the proportion of deaths that were brought-in-dead victims.

(Table 3). Out of the 4696 total RTA deaths in the 8-year period, 1669 deaths (35.43%) were after admission (Table 2) and the remaining 3027 (64.57%) deaths occurred prior to arriving at the hospital.

The major causes of death for all ages at RCH during the year 1406H (1986) are shown in Table 4, with RTA heading the list at 15.2%, followed by cerebrovascular accident 14.3%, malignancy 14.1%, and heart disease 13.8%.

Table 5 demonstrates that the RTA death toll falls most heavily on younger persons, and it was the major cause of death for people under the age of 40 at RCH for 1986, with a rate of 33.8%, followed by burns (10.9%) and carcinoma (9.8%).

TABLE 3. *Overall RTA mortality.*

Year	Total RTA victims seen at RCH	Total RTA deaths	Overall RTA mortality (%)
1400	7192	669	9.30
1401	7595	633	8.33
1402	9294	663	7.13
1403	9632	655	6.80
1404	9031	617	6.83
1405	8157	581	7.12
1406	8552	484	5.66
1407	8521	394	4.62
Total	67,974	4696	6.91

TABLE 4. *Causes of death for all age groups at RCH in 1406.*

Cause	No. (%)
Total	941(100)
RTA	143(15.2)
Cerebrovascular accident	135(14.3)
Malignancy	133(14.1)
Heart disease	130(13.8)
Gastrointestinal tract disease	120(12.8)
Others	280(29.8)

TABLE 5. *Causes of death for patients < 40 years at RCH in 1406.*

Cause	No. (%)
Total	275(100)
RTA	93(33.8)
Burns	30(10.9)
Malignancy	27(9.8)

According to data from the Traffic Statistics Department, the number of cars registered in Riyadh Region was 655,495 in 1400H (1980), and this more than doubled to 1,387,183 by 1407H (1987). The number of recorded vehicular accidents in Riyadh Region also doubled from 8513 in 1400H to 16,678 in 1407H. The increasing number of accidents was directly proportional to the higher number of cars.

Discussion

The number of RTA deaths per 10,000 vehicles per annum in developed countries[5] ranges from the lowest figures of 2.5 in Sweden and 3.1 in the United States to the much higher figure of 144.5 deaths per 10,000 vehicles in a developing country such as Nigeria.[5] The current figure in Riyadh City is in the range of developed countries, with a rate of 4.74 deaths per 10,000 vehicles in 1987.

A large number of RTA victims, 64,942, have been brought to RCH during the 8-year study period. This large number may be due to the number of cars, which is increasing in parallel to the dynamic development of the city. In addition, this is the main general hospital, which receives most of the RTA injuries of the city. Total admissions to the hospital during the 8-year period were over 214,000, and an important percentage of this number was due to RTAs.

The decline of RTA admissions and the increase in the total RTA victims seen at RCH can be explained by the fact that a high percentage of RTA victims received satisfactory treatment in the emergency room and did not require hospital admission. This is due in part to good emergency care and in part to the minor nature of the injuries sustained. The number of brought-in-dead casualties declined despite the marked increase in the number of RTA victims seen at RCH. These improvements may be due to better on-site resuscitation and speedy transportation to the hospital, in addition to better traffic control systems, improved road conditions, safer driving habits, and public education. The average RTA hospital mortality (death after admission) of 2.56% signifies a marked improvement in hospital care at RCH.

Analysis of the major causes of death in 1986 at RCH (Table 5) shows that RTA is at the top of the list for persons under 40 years of age. Similar observations have been made in other studies.[2,3,6] This may be due to the fact that persons of this age group are less affected by other common causes of death, such as malignancy, cerebrovascular accident, and myocardial infarction. Unlike other studies,[6,7] our study showed RTA mortality also as the leading cause of death at RCH (15.2%) for all age groups, though not markedly higher than other causes of death, such as cerebrovascular accident, malignancy, and heart disease (Table 4). A similar study in the United States showed RTA as the third most common cause of death in all age groups.[4,6] This high RTA mortality at RCH could be explained by the fact that RCH alone receives all the prehospital RTA deaths and most of the RTA victims in Riyadh, whereas other medical deaths are shared by hospitals in the city. A rising standard of living has caused the number of cars in the Riyadh region to double in the 8-year study period with a directly proportional increase in RTAs, although mortality steadily diminished.

According to this evaluation the following conclusions can be made. The RTA is the principal cause of death for all age groups in RCH, and the incidence is doubled for individuals under 40 years of age. Fatality rate of RTA after hospital admission has dropped significantly in RCH, and overall RTA mortality in Riyadh has dropped despite the increasing number of RTA injuries. Although the majority of RTA fatalities occur before the victims reach the hospital, the total number of RTA prehospital deaths in Riyadh diminished steadily in the 8-year study period. Higher number of accidents is directly proportional to the increased number of cars.

On the basis of this study and the preceding conclusions, we have formulated the following recommendations:

1. Teaching of traffic rules and safety measures in the schools and through television programs.
2. Encouragement of national research programs for analysis of deaths due to RTAs and promotion of better emergency service.
3. Enforcement of use of preventive measures like seat belts, infants' and children's car seats, prohibition of children to sit in the front seats, and crash helmets for riders of two-wheel vehicles.
4. Strict surveillance and enforcement of penalties for traffic infringements.

Acknowledgment

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References

1. Mufti MH, Koushki PA, Ali JA. Road traffic accident mortality in Riyadh, Saudi Arabia. Ann Saudi Med 1986;6(4):263-4.
2. Kreis DJ Jr, Plasencia G, Augenstein D, et al. Preventable trauma deaths, Dade County, Florida. J Trauma 1986;26(7):649-53.
3. Baker CC, Oppenheimer L, Stephens B, et al. Epidemiology of trauma deaths. Am J Surg 1980;140(1):144-50.
4. Leading causes of death, United States 1982 estimate, Heartfacts 1985 (AHA publication 55-005-1). In: Instructors manual for basic life support, 1985:171.
5. Jacobs GD. Road accident fatality rates in developing countries: a reappraisal. Transport and Road Research Laboratory, Overseas Unit. Presented at the 14th annual summer meeting, PTRC conference, University of Sussex, England, 1986.
6. Somers AR. Life-style and health. In: Last JM, ed. Maxcy-Rosenau public health and preventive medicine, 11th ed. New York: Appleton-Century-Crofts, 1980;1046-65.
7. Dunn EL, Berry PH, Cross RE Jr. Community hospital to trauma center. J Trauma 1986;26(8):733-7.

PERCENTAGE OF DISTAL INTERPHALANGEAL JOINT AFFECTION IN RHEUMATOID ARTHRITIS IN RELATION TO AGE

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تم فحص المفاصل القاصية بين السلاميات في ١٠٠ مريض يعانون من التهاب المفاصل الرثياني المؤكد أو التقليدي لتقصي الإصابة بالتآكل الهامشي وتضيق المسافة المفصلية. وتبين أن نسبة ١٥٪ يعانون من أصابة المفصل القاصي بين السلاميات وكانت الإصابة متناظرة في ١٠ من هؤلاء المرضى الخمسة عشر. كانت المفاصل الرسغية مصابة في جميع حالات اصابة المفاصل القاصية بين السلاميات. كان متوسط أعمار مرضى التهاب المفاصل الرثياني مع اصابة المفاصل القاصية بين السلاميات ٥٠ر٦ عام ومتوسط استمرارية الداء ١٠ر٦ عام، مما يدل على ان تآكل المفصل القاصي بين السلاميات يحدث في المرضى كبار السن الذين يعانون منذ أمد بعيد من التهاب المفصل الرثياني.

The distal interphalangeal (DIP) joints of 100 patients with definite or classical rheumatoid arthritis were studied for marginal erosions and joint narrowings. Fifteen percent had DIP joint affection, and symmetric involvement was present in 10 of these 15 patients. The carpal joints were involved in all cases of DIP affection. The mean age for patients with rheumatoid arthritis and DIP affection was 50.6 years, and the mean duration of disease was 10.6 years, pointing to the fact that DIP joint erosion occurs in older patients with longstanding rheumatoid arthritis.

The distal interphalangeal (DIP) joint has been reported to be affected radiologically in 16% of patients with rheumatoid arthritis after excluding patients with roentgenographic features of degenerative joint disease.[1] The DIP joints may be involved clinically in an important number of patients with rheumatoid arthritis, but erosive changes have been observed less frequently.[2]

Involvement of the DIP joints is not necessarily symmetric. Clarifying this point may eliminate diagnostic confusion since roentgenographic symmetry in rheumatoid arthritis for other small joints is a usual finding.

Patients and Methods

Patients with classical or definite rheumatoid arthritis (by American Rheumatism Association criteria) were selected for the study. Psoriatic cases were excluded from the study as well as patients with secondary osteoarthritic changes.

Standard posteroanterior roentgenographs of both hands were done for all patients and then interpreted by two observers. Marginal erosions and joint narrowing of the second, third, fourth, and fifth DIP joints were screened in all roentgenograms. Any erosion read by the two observers was sufficient to qualify that joint as affected. The percentage of involvement of the carpal, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints was determined. Symmetry of involvement was also recorded.

Results

One hundred patients with rheumatoid arthritis were selected. Their ages varied from 18 to 71 years with a mean of 45.2 years, and the duration of disease ranged from 6 months to 20 years with an average of 6.8 years.

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Erosions were present in DIP joints in 15% of patients (Figure 1). Symmetric involvement was present in 10 of 15 affected patients (66%). Most of the affection occurred in the third joint, especially in the right hand. The fourth joint ranked next in degree of involvement. Carpal joints were affected in all 15 patients with DIP affection.

In the hand joints of the 100 patients, the carpal joints were affected in 68%, PIP joints in 40%, and the MCP joints in 28% of all cases. Joint narrowing was present in only 10% of roentgenograms.

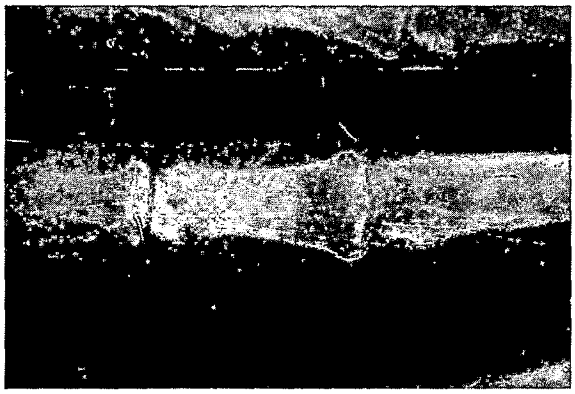

FIGURE 1. Roentgenogram of the third DIP joint showing erosions in a patient with rheumatoid arthritis.

There was only one patient in whom the DIP joints were destroyed, especially the second, third, and fourth joints. In this patient, all PIP joints were destroyed in different degrees.

The mean age for the patients with DIP joint erosions was 50.6 years, and the mean duration of disease was 10.6 years.

Discussion

The percentage of DIP joint affection in this work agrees with the results obtained by Halla et al,[1] where they found the percentage of involvement 16%. The question of symmetry in DIP joint erosion remains important, although not as pronounced as in others, such as the MCP joints.[3]

Narrowing of the joints appears to be of minor importance since flexion of the DIP joints occurs frequently in the hands of patients with rheumatoid arthritis as a step in the production of swan-neck deformity, and this may contribute to the apparent narrowing.

Erosion of the DIP joints increases with the increase in patient age and duration of disease, and this may suggest that erosive changes are present more often in patients with longstanding rheumatoid arthritis.

Acknowledgment

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References

1. Halla JT, Fallahi S, Hardin JG. Small joint involvement: a systematic roentgenographic study in rheumatoid arthritis. Ann Rheum Dis 1986;45(4):327-30.
2. McCarthy DJ Jr, Gatter RA. A study of distal interphalangeal joint tenderness in rheumatoid arthritis. Arthritis Rheum 1966;9:325-36.
3. Bywaters E. The early radiological signs of rheumatoid arthritis. Bull Rheum Dis 1960;11:231-4.

ACCIDENTAL POISONING OF CHILDREN IN QATAR

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تعتبر حالات التسمم العرضي للأطفال من الأسباب المهمة للأمراض والتي يمكن تجنبها. تستعرض هذه الدراسة مراجعة حالات ثلاثمائة وستين طفلا تراوحت أعمارهم من اسبوعين الى عشرة سنوات وعولجوا من التسمم العرضي في مستشفى حمد العام بدولة قطر - كانت أعمار مانسبته ٩١٪ منهم تقل عن أربع سنوات. وكان التوزيع بين الذكور والاناث متعادلا ولم نلاحظ وجود أي نمط فصلي محدد. لم تحدث المواد المبتلعة أعراضا لدي ما نسبته ٣٠ر٥٪ وظهرت الأعراض السريرية لدى مانسبته ٥١ر٧٪ وتراوحت بين الخفيفة والمعتدلة بنما ظهرت أعراض شديدة لدى ما نسبته ١٧ر٨٪. شكلت الأدوية نسبة غالبة من المواد المبتلعة (٧٦ر٩٪) وتلتها بنسب متفاوتة المواد الهايدروكربونية، الكيماويات والمنتجات المنزلية. أدى التسمم الى الوفاة في حالة واحدة وحدثت معاودة التسمم في حالة أخرى. ركزت الدراسة على ضرورة نشر الوعي بحالات التسمم عن طريق الاعلام ومراكز الرقابة لتفادي مثل هذه الأمراض التي تلحق بالأطفال.

Accidental poisoning of children is an important and preventable cause of morbidity. This is a report of a retrospective study of 360 children aged 2 weeks through 10 years with accidental poisoning seen at Hamad General Hospital in the State of Qatar. Ninety-one percent of these children were below 4 years of age. An equal male-female distribution and no specific seasonal pattern were found. Ingestion occurred with no symptoms in 30.5%, mild-to-moderate clinical manifestations in 51.7%, and severe manifestations in 17.8%. Drugs were the most common substance ingested (76.9%), followed in decreasing frequency by hydrocarbons, chemicals, and household products. There were one fatal case and one recurrence. The study reinforced the need to teach poisoning awareness through poison information and control centers to prevent this childhood morbidity.

Accidental poisoning due to ingestion of potentially toxic substances is a major cause of morbidity in children worldwide.[1-5] In the United States, the introduction of the Poison Prevention Packaging Act of 1970 and the use of child-restraint containers and packaging for some medicines in the United Kingdom have lead to a marked decrease in such poisoning. In view of increasing use and availability of drugs in Qatar, the problem of poisoning is likely to increase unless methods for prevention are adopted.

The purpose of this study was to determine the prevalence and pattern of ingestion of potentially toxic substances by children in the State of Qatar and to recommend plans for poisoning prevention.

Patients and Methods

Medical records of patients admitted to the pediatrics department in Hamad General Hospital because of accidental poisoning during a 3½-year period (January 1983 to May 1986) were reviewed. Data were gathered concerning patient nationality, age, and sex, form of accidental poisoning, extent of symptoms, length of time between poisoning and medical attention, and length of hospital stay.

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The term poisoning in this context refers to all exposures to potentially toxic products whether or not the exposure resulted in symptoms.

Results

A total of 16,880 children were admitted to the pediatrics department between January 1983 and May 1986. Ingestion of potentially toxic substances with or without symptoms was seen in 360 patients (2.1% of pediatric admissions). Qataris constituted 194 cases (53.9%). Of the total, 328 patients (91.1%) were 4 years of age or less (Table 1). Of Qatari patients, 62.4% were less than 2 years old while 51.2% of patients of other nationalities were less than 2 years old. There were 188 males and 172 females with male-female ratio of 1.1:1.0. A total of 71.1% of patients were seen in the accident and emergency department, and the rest were referred from health centers. No specific seasonal distribution was evident.

Drugs were the most commonly ingested substance in 277 patients (76.9%), followed by hydrocarbons (kerosene) in 49 (13.6%), chemicals in 18 (5.0%), and household products in 16 (4.4%). The percentage of patients who had ingested more than one drug was 3.6%.

TABLE 1. *Age distribution.*

Age (y)	No.(%)
0–2	206(57.2)
3–4	122(33.9)
5–6	18(5.0)
7–8	10(2.8)
9–10	4(1.1)

TABLE 2. *Classes of symptoms.*

Symptoms	No.(%)
Asymptomatic	110(30.5)
Mild-to-moderate symptoms	186(51.7)
Drowsiness	68
Vomiting	78
Cough without dyspnea	19
Mild tachypnea	121
Severe symptoms	64(17.8)
Convulsion	16
Myoclonic jerks	20
Extreme irritability	16
Coma	6
Dyspnea, marked tachypnea	6
Total patients	360

Ingestion without symptoms occurred in 110 patients (30.5%), mild-to-moderate clinical manifestations occurred in 186 patients (51.7%), and severe manifestations in 64 patients (17.8%) (Table 2).

Among the 277 patients who ingested drugs, 11.2% ingested antihistaminics and decongestants; 9.0%, antiemetics; 7.6%, salicylates; 7.2%, hypnotics and sedatives; 7.2%, anticonvulsants and antidepressants; and 4.7%, tranquilizers (Table 3).

Twenty-one of the 25 patients who ingested antiemetics took metoclopramide; the majority (13 of 25) were below 9 months of age and were mostly given suppositories or drops to relieve vomiting. The commonest presentation was oculogyric crisis, followed by abnormal movement, drowsiness, and superficial coma.

Salicylate (aspirin) ingestion accounted for 21 patients (7.6%) with drug poisoning. Most cases had simple ingestion, and only two patients had clinical manifestations with toxic levels, and they received appropriate medical treatment.

Of the 49 patients who ingested kerosene, most had respiratory symptoms (33 of 49, or 67.3%). Seventeen of 49 had chemical pneumonitis, with complicated pneumonia with effusion in four patients, and pneumothorax in one. Most patients were given antibiotics to prevent secondary bacterial infection.

The chemical group comprised 18 patients, 5% of poisonings. Organophosphate (insecticide) and rat poisoning ingestion occurred in 13 patients. Patients who ingested rat poisoning were asymptomatic, while the majority of patients with organophosphate poisoning had a typical picture of altered consciousness and constricted pupils. Other chemicals ingested were potassium permanganate (two patients), and iodine, glue, and lead (one patient each).

Household products accounted for 4.4% of all poisonings (16 patients). Poisoning with detergent, chlorine bleach, and antiseptic compounds occurred in half of these cases. One patient developed esophageal stricture after ingestion of sodium hypochlorite solution. The majority of

TABLE 3. *Delay in seeking medical care and length of hospital stay after drug ingestion.*

	Patients	Delay (min)		Hospital stay(d)	
Name/type of drug	No.(%)	Mean	SD	Mean	SD
Salicylates	21(7.6)	168	169	4.6	5.5
Iron	9(3.2)	284	340	2.4	4.1
Tranquilizers	13(4.7)	214	236	1.9	0.6
Antiemetics	25(9.0)	148	114	3.6	2.4
Antidepressants	10(3.6)	180	176	2.8	1.5
Aminophylline	4(1.4)	65	0	2.5	1.1
Antihypertensives	8(2.9)	155	145	4.2	4.0
Antibiotics	9(3.2)	84	56	2.1	1.0
Anticonvulsants	10(3.6)	301	308	1.9	0.6
Antihistamines and decongestants	31(11.2)	147	184	2.8	1.5
Anticholinergics	14(5.0)	108	66	1.9	0.8
Hypnotics and sedatives	20(7.2)	173	220	2.2	1.3
Vitamins	10(3.6)	106	128	1.7	0.8
Nonsteroidal anti-inflammatories	9(3.2)	61	65	2.0	2.3
Others	50(18.0)	153	266	3.9	5.8
Unknown	34(12.3)	149	142	3.9	5.8
Total	277				

patients who ingested bleach had burns in the mouth managed by antibiotic and hydrocortisone treatment. Other household products ingested were perfume, shampoo, almond oil, castor oil, hair oil, and air freshener.

The mean duration of delay in seeking medical advice and length of hospital stay are detailed in Table 3. The mean duration from exposure to treatment was 147 minutes, 157 minutes for Qatari males and 143 minutes for Qatari females. The delay for drugs was 157 minutes; hydrocarbons, 150 minutes; household products, 84 minutes; and chemicals, 55 minutes. The mean duration of delay was longest for anticonvulsants, 301 minutes, iron, 284 minutes, and tranquilizers, 214 minutes. The mean length of hospital stay was 3.3 days. For Qatari females it was 2.4 days, while for males 4.1 days. The mean duration of hospital stay was 2.9 days for drug ingestion, 5.2 days for hydrocarbons, 4.6 for household products, and 3.1 days for chemical materials. The mean duration of hospital stay after drug ingestion was longest for salicylates, 4.6 days, and antihypertensives, 4.2 days.

None of the patients received first aid management at home with ipecac syrup. Recurrence of ingestion occurred in one patient during the study period. A 6-month-old boy died of aminophylline toxicity after being given aminophylline suppositories (250 mg) in a health center.

Discussion

Ingestion of potentially toxic substances is a major cause of hospital admission, 2.1% of pediatric admissions in this study. The number of children admitted with this diagnosis was higher than has been reported from other countries.[6] This may be explained by the liberal admission policy and other patterns of medical care, rather than true geographical difference in the incidence of accidental poisoning in childhood.

The high preponderance of accidental poisoning under 4 years of age is similar to other reports. The male-female ratio was equal in contrast to other studies where male preponderance was noted.[7] There was no specific seasonal pattern, which is similar to the observations[8] of others.

The spectrum of commonly ingested substances observed in the present study seems at marked variance with that of previous reports from Saudi Arabia. In our study, drug ingestion was most common. Following in decreasing order were hydrocarbons, chemicals, and household products. Another Saudi study noted hydrocarbons first, followed by household products and

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drugs.[9,10] A third Saudi study cited drugs followed by household products in incidence.[11] As in our study, studies in the United States found drugs to be the most commonly ingested cause of poisoning in children.[12]

The reasons for regional variation are not clear, but may be related to sociocultural differences, regulation of drug distribution, and other economic factors. In the State of Qatar, institutional health care is readily accessible and free of charge, and drug prescriptions are easily obtained and filled in health centers.

An interesting finding in our study related to the severity of clinical manifestations; 30.5% were asymptomatic, 51.7% had mild-to-moderate symptoms, and 17.8% had severe symptoms. This is in contradistinction to studies in the United States which showed only 10% of patients with symptoms.[3] Also, the severity of signs and symptoms is reported to be less marked in the United States with 71% asymptomatic and 29% with clinical manifestations. The exact explanation is not known but may be related to the high percentage of drug poisoning in Doha, delays in arrival, and the type of drug poisoning involved.

Chemical pneumonitis was diagnosed in 34.7% of cases of kerosene ingestion. This finding contrasts with lower complication rates in other reports[13] but is similar to reports from Saudi Arabia.[9]

Of interest is that a high percentage of the ingested drugs (34 cases, or 12.3%) were unknown. This is quite similar to that reported in Saudi Arabia.[10]

Antiemetic ingestion, specifically metochlopromide, caused significant morbidity. The majority of patients were under 9 months old.

The factors responsible for failure to identify the ingested drugs and chemicals are many. This points to the need for both clear legislation concerning dispensing drugs in properly labeled, child-proof containers and the continuing education of parents and caretakers on keeping all drugs in their original containers.

Although early recognition and improved therapy are important goals, there is an apparently serious deficit in well-recognized strategies for prevention of poisoning. Such strategies include universal safety packaging, public education, physician education not only in management but also encouragement of preventive measures, and restraint in the prescription of unnecessary or ineffective medications. Poison information and control centers, proved effective in other parts of the world, should be established. This study has reaffirmed that teaching of poisoning awareness and prevention should be a standard of pediatric care.

References

1. Lawson GR, Craft AW, Jackson RH. Changing pattern of poisoning in Newcastle, 1974-81. Br Med J 1983;287(6384):15-7.
2. Sibert JR, Minchom PE, Craft AW, et al. Child resistant containers really are effective (letter). Lancet 1979;2:522.
3. Bahamon CC, Lovejoy FH Jr. Effectiveness of a regional poison center in reducing excess emergency room visits for children's poisonings. Pediatrics 1983;72(2):164-9.
4. Walton WW. An evaluation of the Poison Prevention Packaging Act. Pediatrics 1982;69(3):363-70.
5. Pearn J, Nixon J, Ansford A, Corcoran A. Accidental poisoning in childhood: five year urban population study with 15 year analysis of fatality. Br Med J 1984;288(6410):44-6.
6. White LE, Driggers DA, Wardinsky TD. Poisoning in childhood and adolescents: a study of 111 cases admitted to a military hospital. J Fam Pract 1980;11(1):27-31.
7. Basavaraj DS, Forster DP. Accidental poisoning in young children. J Epidemiol Community Health 1982;36(1):31-4.
8. Andersen JA, Narasimhan MJ. Drug and chemical poisoning. In: Nelson's textbook of pediatrics. Philadelphia: WB Saunders 1975:1660-1.
9. Mahdi AH, Taha SA, Al-Rifai MR. Epidemiology of accidental home poisoning in Riyadh (Saudi Arabia). J Epidemiol Community Health 1983;37:291-5.
10. El-Mouzan MI, Elageb A, Ali NK. Accidental poisoning of children in the Eastern Province. Saudi Med J 1986;7(3):231-6.
11. Khalil MAK. Accidental poisoning in Saudi children seen at Riyadh, Al-Karj Military Hospital. Saudi Med J 1986;7(6):613-7.
12. McIntire MS. Safety packing: a model for successful accident prevention. Pediatr Ann 1977;6(11):706-8.
13. Anas N, Namasonthi V, Ginsburg CM. Criteria for hospitalizing children who have ingested products containing hydrocarbons. JAMA 1981;246(8):840-3.

PATHOLOGY OF BRUCELLOSIS: A REVIEW OF 88 BIOPSIES

Mohammed Akhtar, MD, FCAP; M. Ashraf Ali, MD, FRCPC, FCAP

تم فحص ما مجموعه ٨٨ خزعة تمثل نوعيات مختلفة من الأنسجة تم أخذها من ٧٨ مريضا يعانون من إصابات مؤكدة بالبروسيلة. كان النمط النسيجي الأكثر تواردا يتسم بالالتهاب المزمن غير النوعي ويتميز بالارتشاح اللمفي مع اعداد متباينة من المنسجات والخلايا المصورية. كانت معدلات الاصابة بالالتهاب الحبيبي والنخر الحاد والالتهاب القيحي أقل تواردا. لم نتمكن من تحديد أية مظاهر شكلية خاصة بالالتهاب الجرثومي بالبروسيلا في أي من الخزعات المأخوذة.

A series of 88 biopsy specimens representing a large variety of tissues from 78 proved cases of brucellosis were reviewed. The most frequent histologic pattern was that of nonspecific chronic inflammation characterized by lymphocytic infiltration with variable numbers of histiocytes and plasma cells. Granulomatous inflammation and acute necrotizing and suppurative inflammation were encountered less frequently. In none of the biopsies could any morphologic features specific for *Brucella* infection be identified.

Brucellosis is a fairly common disease in Saudi Arabia. In recent years, several studies describing the clinical aspects of the disease have been published from various institutions in this country.[1-5] However, none of these studies has described the histopathologic features of various lesions in patients with brucellosis. The purpose of this study is to review the morphologic features in a series of biopsies from patients with brucellosis seen in our laboratories and review the relevant literature.

Materials and Methods

All cases diagnosed as brucellosis at King Faisal Specialist Hospital and Research Centre during the 6-year period from January 1980 to December 1985 were identified. Among these patients a subgroup was selected in which tissue biopsy specimens from various locations were available. Only those cases in which a brucella titer of 1:160 or higher was demonstrated and in which the biopsy material was obtained within 6 months of the diagnosis were included in the study. Those cases in which the tissue removed was obviously unrelated to brucella infection (such as hernial sac, lens, and neoplasms) were excluded.

A total of 88 biopsy specimens from 78 patients with brucellosis were thus included in the study. Sites of these biopsies are given in Table 1.

The resected tissues were fixed in 10% buffered formaldehyde solution and following dehydration were embedded in paraffin in the usual manner. Four-micron sections were stained by hematoxy-

TABLE 1. *Sites of biopsies.*

Sites	No.
Liver	15
Bone marrow	16
Bone and cartilage	13
Cardiac valves	11
Soft tissues	5
Gastrointestinal tract	4
Joints	5
Lymph nodes	5
Skin	3
Body cavity	3
Miscellaneous	8

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lin and eosin. Special stains, such as PAS, AFB, and Brown Brenn stains, were performed when indicated.

Results

Of the 15 liver biopsy specimens, six revealed nonspecific hepatitis characterized by an increase in the numbers of Kupffer cells and histiocytes lining the sinusoids. This was associated with an inflammatory infiltrate consisting of lymphocytes within the portal areas and focal necrosis of liver cells within the hepatic lobules (Figure 1).

Granulomatous inflammation of the liver was present in four specimens. Two of these contained microgranulomas consisting of small aggregates of histiocytes and lymphocytes (Figure 2). The remaining two specimens contained macrogranulomas composed of epithelioid cells, lymphocytes, and occasional multinucleated giants (Figure 3). There was no caseation although early necrosis was seen in some of the granulomas.

In four biopsies features of chronic active hepatitis were noted. There was moderately dense infiltration of portal areas by lymphocytes associated with piecemeal necrosis and early portal fibrosis (Figure 4). One specimen revealed cirrhosis.

Sixteen bone marrow biopsies revealed a variety of histologic alterations. The most common finding was hyperplasia of some or all the elements of the bone marrow identified in nine specimens. Granulomas were present in only four specimens (Figure 5). In two patients the bone marrow appeared hypocellular, and one specimen showed infiltration.

Ten cardiac valves were examined (six aortic and four mitral). Of these, four revealed chronic inflammation and fibrosis associated with marked deformities of the valves. Focal calcification was also present in two of these valves. The morphology in these valves was indistinguishable from that of old healed rheumatic valvulitis (Figure 6). In three additional cases varying degrees of infiltration by chronic inflammatory cells (predominantly lymphocytes) was noted. These three valves revealed small vegetations on the endocardial surface (Figure 7). The vegetations were composed of fibrinous material in which small aggregates of lymphocytes and polymorphonuclear cells were

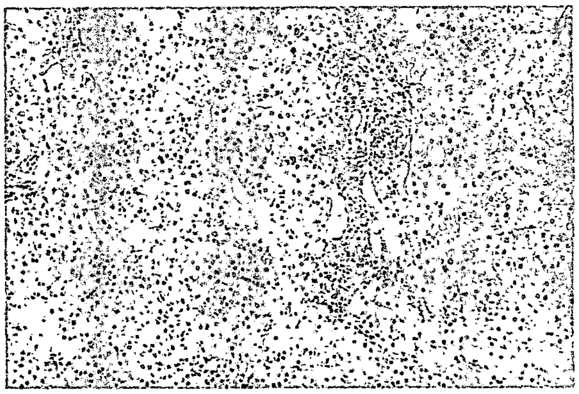

FIGURE 1. Liver biopsy specimen showing nonspecific reactive hepatitis. There is lymphocytic infiltration in the portal area, prominent Kupffer cells, and a smaller aggregate of lyphocytes within the liver lobule (hematoxylin and eosin stain, original magnification, × 150).

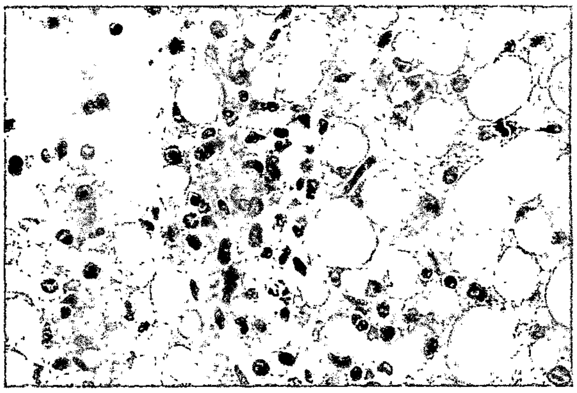

FIGURE 2. Liver biopsy specimen from a patient with brucellosis showing microgranulomas consisting of lymphocytes and histiocytes. Moderate fatty changes are also present (hematoxylin and eosin stain, original magnification, ×200).

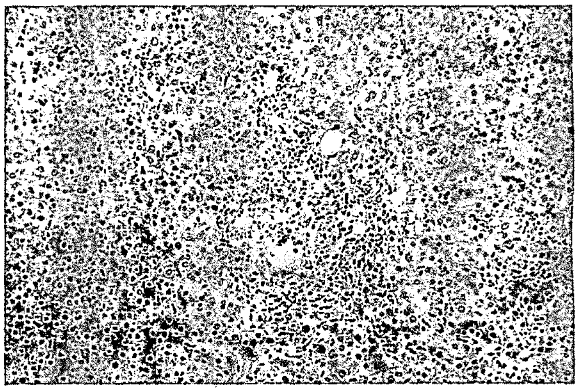

FIGURE 3. Liver biopsy specimen showing a macrogranuloma composed of epithelioid cells and giant cells (hematoxylin and eosin stain, original magnification, ×150).

present, and varying degrees of organization within these vegetations were also noted. No bacterial organisms could be demonstrated using special stains. Three valves showed no inflammation. One additional specimen was a Hancock valve prosthesis which was not examined histologically. The patient, however, had a positive blood culture for brucella.

Five specimens from soft tissues were examined. Three of these revealed chronic nonspecific inflammation characterized by the presence of lymphocytes, plasma cells, and occasional polymorphonuclear cells and histiocytes. In the remaining two biopsies, there was chronic inflammation similar to that described above, but in addition, there were scattered granulomas composed of epithelioid cells (Figure 8), but no central caseation or necrosis. Thirteen specimens were from bones and cartilagenous tissues. Of these, seven showed chronic nonspecific inflammation, while three revealed chronic inflammation with occasional epithelioid granulomas without evidence of necrosis (Figures 9 and 10). All were associated with varying degrees of bone destruction and new bone formation. Special stains for bacteria including acid-fast bacilli as well as fungal organisms were negative. In three biopsies no significant inflammation was encountered.

Three skin biopsies were examined. Two of the specimens revealed focal dermal infiltration by lymphocytes. The third showed a mild lymphocytic and histiocytic perivascular infiltration in the dermis (Figure 11). No granulomas were seen.

Similar changes were noted in several other locations such as the gastrointestinal tract, joints, lymph nodes, and testes. The details of these biopsies are given in Table 2. A variety of other tissues showing changes probably unrelated to brucella infection were also noted (Table 3).

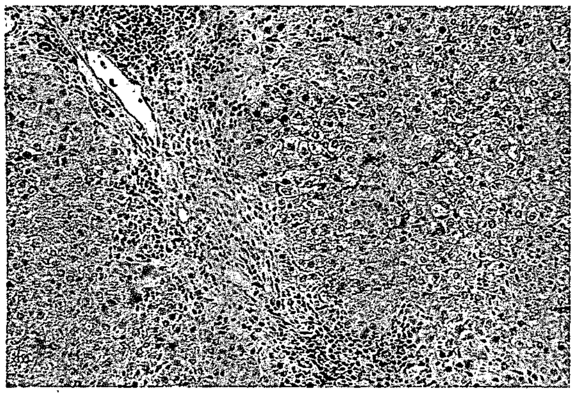

FIGURE 4. Liver biopsy specimen featuring portal infiltration by lymphocytes, piecemeal necrosis, and fibrosis (hematoxylin and eosin stain, original magnification, ×150).

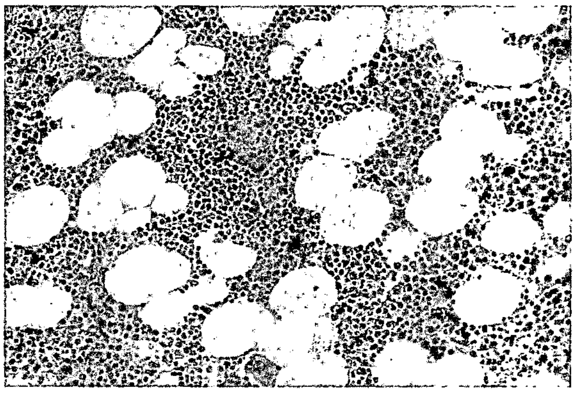

FIGURE 5. Trephine biopsy specimen of bone with normocellular bone marrow and a solitary epithelioid granuloma (hematoxylin and eosin stain, original magnification, ×150).

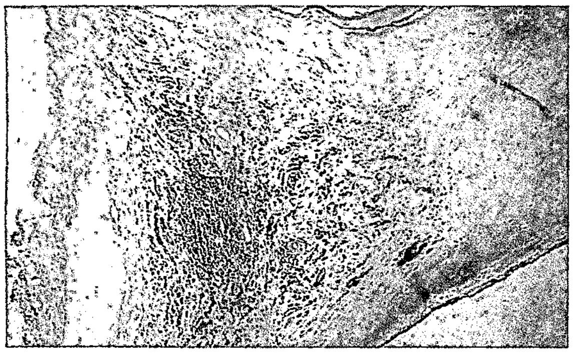

FIGURE 6. Aortic valve specimen from a patient with brucella endocarditis showing fibrosis, vascular proliferation, and inflammatory cell infiltration (hematoxylin and eosin stain, original magnification, ×100).

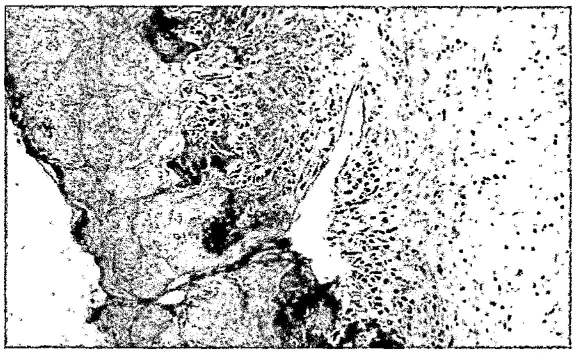

FIGURE 7. Aortic valve specimen with brucella endocarditis. The endocardial surface is covered by a large vegetation composed of fibrinous material (hematoxylin and eosin stain, original magnification, ×100).

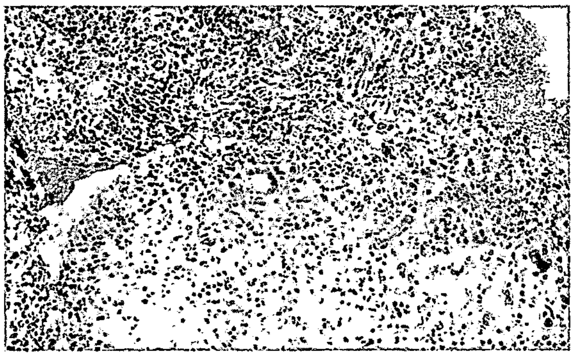

FIGURE 8. Biopsy specimen from an abscess in the soft tissues of a patient with brucellosis. There is granulation tissue with chronic inflammation, and scattered epithelioid cells and giant cells are also present (hematoxylin and eosin stain, original magnification, ×150).

TABLE 2. *Pathology of brucellosis.*

Site/source of specimen	Pathologic findings	No.
Gastrointestinal tract (1 esophagus, 1 duodenum, 3 gastric mucosa)	Chronic nonspecific inflammation	5
Joints		
Tissue biopsy	Chronic nonspecific inflammation	1
	Granulomatous inflammation	1
	Rheumatoid synovitis	1
Synovial fluid	Polymorphonuclear cells	1
	Lymphocytosis	1
Lymph nodes	Nonspecific hyperplasia	3
	Dermatopathic lymphadenitis	1
	Granulomatous inflammation	1
Body cavities		
Tissue biopsy	Chronic inflammation	1
Fluid	Lymphocytosis	1
	Mesothelial cells	2
Testes	Undescended testes	1
	Necrotizing acute inflammation	1

TABLE 3. *Pathology of brucellosis in miscellaneous tissues.*

Site/source of specimen	Pathologic findings	No.
Uterus	Proliferative endometrium	1
Products of conception	Inflammation and necrosis	3
Appendix	Acute appendicitis	1
Salivary gland	Chronic inflammation	1
Aortic aneurysm	Atherosclerosis	1
Aortic graft	Gross examination only	1

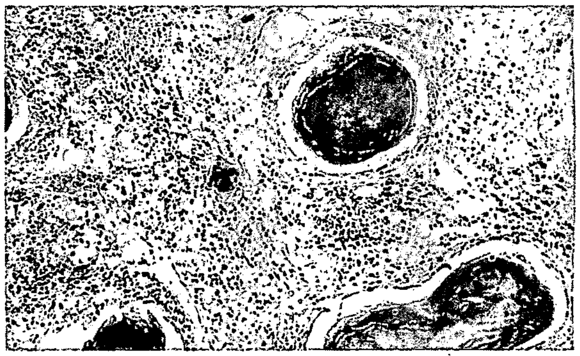

FIGURE 9. Bone biopsy specimen in a patient with brucellosis showing intertrabecular fibrosis along with infiltration by inflammatory cells predominantly lymphocytes (hematoxylin and eosin stain, original magnification, ×100).

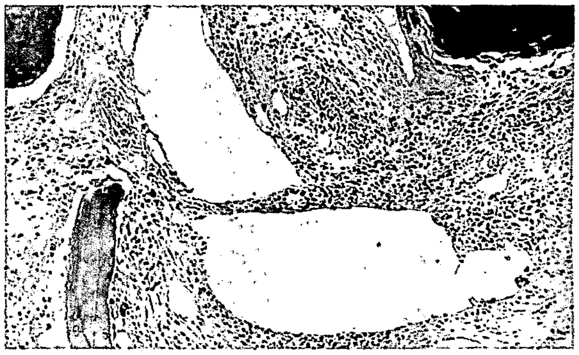

FIGURE 10. Bone biopsy specimen featuring intertrabecular fibrosis with chronic inflammation. An epithelioid granuloma is present (hematoxylin and eosin stain, original magnification, ×150).

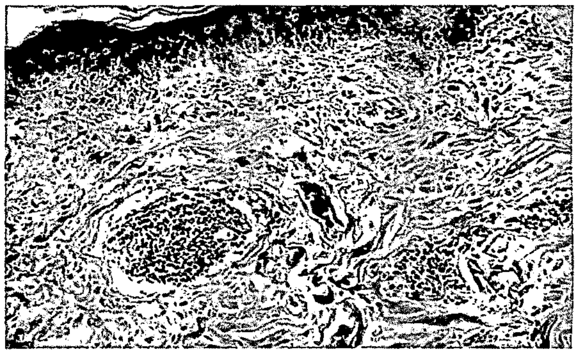

FIGURE 11. Skin biopsy specimen showing a lymphocytic and histiocytic infiltrate around the dermal vessels (hematoxylin and eosin stain, original magnification, ×150).

Discussion

Brucella organisms enter the body by penetrating the intact mucosa or injured skin at locations such as hands, arms, oropharynx, conjunctiva, and lung. If the inoculum is small, it is quickly phagocytosed by polymorphonuclear cells and histiocytes and is eliminated either at the site of entry or within the regional lymph nodes. In cases where the inoculum is large, local and regional defense mechanisms may be unable to contain the infection so that some of the organisms may enter the blood stream and cause bacteremia. In the blood stream, the organisms are quickly phagocytosed and are then carried to organs rich in reticuloendothelial cells such as liver, spleen, and lymph nodes where the organisms may be completely eliminated. Inability to kill all the organisms usually results in formation of epithelioid granulomas in these organs. The granulomas may suppurate and release organisms in the blood stream resulting in bacteremia. Persistent and recurrent episodes of bacteremia usually result in secondary localization of the *Brucella* organisms in a variety of tissues such as heart, soft tissues, genitourinary system, and musculoskeletal system.[6]

Most of the pathologic lesions of human brucellosis are due to proliferation of bacterial organisms within the tissues. This may be at the site of local inoculation, within the organs of regional and systemic defense, or in sites of secondary localization of organisms. In addition to these inflammatory lesions, pathologic changes secondary to immunologic injury may also be encountered. Thus, vasculitis involving the skin and other organs as well as occasional cases of glomerulonephritis are probably due to deposition of immune complexes rather than the presence of *Brucella* organisms within these tissues.[7-13]

Involvement of the liver is a frequent complication of human brucellosis. The most commonly described pathology in liver biopsy specimens from patients with brucellosis is nonspecific reactive hepatitis. In some cases, however, the liver biopsy may reveal features of granulomatous hepatitis.[14-18] The factors determining the presence or absence of granulomas within the liver biopsies in human brucellosis are poorly understood. The duration of the disease may be important, with granulomas more likely to occur in disease of shorter duration. It has also been noted that granulomas are more likely to occur in infections with *B. abortus* and *B. suis*, as compared to *B. melitensis*.[14-18]

Occasional patients with brucella infection may show cirrhosis. An etiologic relationship between brucella infection and cirrhosis was initially suggested but could not be substantiated in subsequent studies.[14,19] One patient in our study had cirrhosis, though this was probably unrelated to brucellosis. Chronic active hepatitis was seen in four of our biopsies. Such a lesion has not been previously reported in association with human brucellosis. Therefore, it is not clear whether this was merely coincidental or there was an etiologic relationship. Three of our patients were positive for hepatitis surface antigen. Therefore, presumably chronic active hepatitis in these patients was unrelated to brucellosis and was perhaps a reflection of the high incidence of chronic active hepatitis in our patient population.[20]

Involvement of the heart in brucellosis is uncommon but is an important cause of death in fatal brucella infections. The hallmark of brucella lesions in the heart is endocarditis.[21-23] This may involve the cardiac valves and, if not treated promptly, may ultimately lead to fibrosis, hyalinization, and calcification within the valve, thus producing valvular deformities indistinguishable from those seen in patients with rheumatic valvulitis. Vegetations may also be seen on the endocardial surface of the valves. Special stains for bacteria may occasionally show organisms; however, in a majority of cases, these stains fail to reveal organisms within the vegetations. In vitro cultures from vegetation may also fail to grow organisms. In rare cases, granulomatous inflammation within myocardium may be encountered. These lesions resemble Aschoff bodies seen in acute rheumatic fever.

Skin lesions may occur in 5% to 10% of patients with brucellosis. A large variety of lesions have been observed.[7-10] These may be macular, maculopapular, vesicular, purpuric, and psoriatic. The corresponding histologic appearances have not been fully elucidated. In some patients there is evidence of vasculitis which may be systemic or limited only to skin. Histologically these lesions show granulomatous inflammation closely associated with blood vessels. In other cases there may be perivascular lymphocytic infiltrates in the dermis. In some cases lesions resembling erythema nodosum may be seen in the deeper dermis and subcutaneous tissue. Skin lesions at the site of inoculation in previously unexposed patients are characterized by formation of localized abscesses.

In addition to the lesions of brucellosis described in this study, pathologic changes in a variety of other locations have also been reported in the literature. These include gallbladder, lung, spleen, genitourinary tract, and nervous system.

Involvement of gallbladder in patients with brucellosis has been reported only occasionally.[24] The histologic appearance is that of chronic inflammation with occasional epithelioid granulomas. Pulmonary lesions in patients with brucellosis are uncommon. There may be bronchitis, bronchopneumonia, lung abscess, and empyema.[25] Enlargement of spleen is a common clinical finding in patients with brucellosis. There may be diffuse increase in the numbers of macrophages with scattered granulomas.[21]

Involvement of the genitourinary tract by brucella infection is uncommon. Chronic inflammation of the urinary bladder, prostate, testes, and epididymis with or without granulomas may be seen. Occasionally, there may be acute orchitis with abscess formation. Similar chronic inflammatory infiltration may also be seen in the interstitium of the kidney resulting in the destruction of renal parenchyma thus producing a histologic picture identical to that of chronic pyelonephritis. When granulomas are present, distinction from renal tuberculosis may be difficult.[21,26-29]

Relationship between glomerular disease and human brucellosis remains poorly understood. Diffuse or segmental proliferative as well as sclerosing lesions may be seen in patients with brucella endocarditis. In addition, isolated cases of glomerulopathy in the absence of endocarditis have been reported in recent years. These include diffuse proliferative glomerulonephritis, membranous glomerulonephritis, and IgA nephropathy. These lesions are probably mediated by deposition of immune complexes.[11-13,30]

Involvement of the central nervous system by brucella infection, i.e., neurobrucellosis, appears to be rare.[31,32] There may be syndromes of meningitis, encephalitis, myelitis, and radiculitis. The exact nature of pathology in these patients is not clearly understood since there are very few reports on actual pathology. Pathologic changes in the brain may include vasculitis, diffuse chronic meningitis, and granulomatous meningitis. Inflammation of the cerebral vessels may cause mycotic aneurysms.[25]

In summary, histopathologic features in 88 biopsy specimens from patients with brucellosis have been described and pertinent literature was briefly reviewed. The results from this study as well as review of literature indicate that there are no specific histopathologic patterns characteristic of brucellosis. However, in countries like Saudi Arabia, where brucellosis is endemic, all unexplained inflammatory lesions with or without granulomas should raise suspicion of brucellosis.

References

1. Arrighi HM. Brucellosis surveillance in Saudi Arabia's Eastern Province. Ann Saudi Med 1986;6(4):S-5-10.
2. Haddad Q. Current experience with brucellosis at Security Forces Hospital, Riyadh. Ann Saudi Med 1986;6(4):S-11-14.
3. Khan MY. Brucellosis: observations of 100 patients. Ann Saudi Med 1986;6(4):S-19-23.
4. Al-Marshedy AR, Harland PSEG. Brucellosis in children. Ann Saudi Med 1986;6(4):S-25-27.
5. Al-Freihi HM, Al-Mohaya SA, Al-Mohsen MFA, et al. Brucellosis in Saudi Arabia: diverse manifestations of an important cause of pyrexial illness. Ann Saudi Med 1986;6(2):95-9.
6. Bennett JE. Brucellosis. In: Wyngaarden JB, Smith LH Jr, eds. Cecil textbook of medicine. 17th ed. Philadelphia: WB Saunders, 1985.
7. FrancoVicario R, Balparda J, Santamaria JM, et al. Cutaneous vasculitis in a patient with acute brucellosis. Dermatologica 1985;171(2):126-8.
8. Gee-Lew BM, Nicholas EA, Hirose FM, et al. Unusual skin manifestations of brucellosis. Arch Dermatol 1983;119(1):56-8.
9. Berger TG, Marshall AG, Goette DK. Cutaneous lesions in brucellosis. Arch Dermatol 1981;117(1):40-2.
10. Al-Orainey IO, Siddiqui MA, Wright SC, et al. Skin lesions in brucellosis: report of two cases. Ann Saudi Med 1986;8(3):219-20.
11. Eugene M, Gauvin JB, Roux CH, Barthez JP. A case of acute brucellosis with membranous glomerulopathy (letter). Clin Nephrol 1987;28(3):158-9.
12. Nunan TO, Eykyn SJ, Jones NF. Brucellosis with mesangial IgA nephropathy: successful treatment with doxycycline and rifampicin. Br Med J 1984;288(6433):1802.
13. Abu-Romeh SM, Kozma GN, Sabha JM. Brucella endocarditis causing acute renal failure (letter). Nephron 1987;46(4):388-9.
14. Cervantes F, Bruguera M, Carbonell J, et al. Liver disease in brucellosis: a clinical and pathologic study of 40 cases. Postgrad Med J 1982;58(680):346-50.
15. Young EJ. Brucella melitensis hepatitis: the absence of granulomas. Ann Intern Med 1979;91(3):414-5.

16. Masana L, Bernardo L, Bacardi R, Gaurdia J. Brucella hepatitis (letter). Ann Intern Med 1980;92(5):709.
17. Bruguera M, Cervantes F. Hepatic granulomas in brucellosis (letter). Ann Intern Med 1980;92(4):571-2.
18. Guerrero MLF, Curiel MD, Cansino JMC. Hepatic granulomas in brucellosis (letter). Ann Intern Med 1980;92(4):572.
19. McCullough NB, Eisele CW. Brucella hepatitis leading to cirrhosis of the liver. Arch Intern Med 1951;88:793-802.
20. Kingston ME, Ali MA, Atiyeh M, Donnelly RJ. Diagnosis of chronic active hepatitis: a review of 100 cases. King Faisal Spec Hosp Med J 1984;4(1):9-16.
21. Hunt AC, Bothwell PW. Histological findings in human brucellosis. J Clin Pathol 1967;20:267-72.
22. Peery TM, Belter LF. Brucellosis and heart disease: II. Fatal brucellosis: a review of the literature and report of new cases. Am J Pathol 1960;36:673-97.
23. Ellner JJ, Rosenthal MS, Lerner PL, McHenry MC. Infective endocarditis caused by slow-growing fastidious, Gram-negative bacteria. Medicine 1979;58(2):145-58.
24. Morris SJ, Greenwald RA, Turner RL, Tedesco FJ. Brucella-induced cholecystitis. Am J Gastroenterol 1979;71(5):481-4.
25. Young EJ. Human brucellosis. Rev Infect Dis 1983;5(5):821-42.
26. Abarnathy RS, Price WE, Sprink WW. Chronic brucellar pyelonephritis simulating tuberculosis. JAMA 1955;159:1532-7.
27. Forbes KA, Lowry EC, Gibson TE, Soanes WA. Brucellosis of the genitourinary tract: review of the literature and report of a case in a child. Urol Surv 1954;4:391-412.
28. Kelalis PP, Greene LF, Weed LA. Brucellosis of the urogenital tract: a mimic of tuberculosis. J Urol 1962;88:347-53.
29. Dunea G, Kark RM, Lannigan R, et al. Brucella nephritis. Ann Intern Med 1969;70:783-90.
30. Doregatti C, Volpi A, Torri Tarelli L. Acute glomerulonephritis in human brucellosis (letter). Nephron 1985;41(4):365-6.
31. Bashir R, Al-Kawi MZ, Harder EJ, Jinkins J. Nervous system brucellosis: diagnosis and treatment. Neurology 1985;35:1576-81.
32. Panayiotopoulos CP. Neurobrucellosis: a cause for concern and action. Ann Saudi Med 1988:8(3):167-8.

DEFECTIVE ARGININE-INDUCED INSULIN SECRETION IN CHILDREN WITH NUTRITIONAL RICKETS

Ashraf T. M. Soliman, MD; Mohamed K. Aref, MD; Abd El-Hadi I. Hassan, MD

تم تقييم الافراز المستحث بالأرجنين للأنسولين وهورمون النمو لدى عشرة أطفال مصابين بالرخد الناجم عن عوز فيتامين «د» وقورنت القيم بتلك التي حصلنا عليها من مجموعة ضابطة مكونة من ثمانية أطفال أسوياء من أعمار مماثلة. بلغ متوسط مستوى الأنسولين في المصل بعد ثلاثين دقيقة من التسريب الوريدي لهيدوركلوريد الأرجنين (١٠٪ محلول، ٠٫٥ غم/كغم). ٣ ، ١٥٩ ± ١٢٢٫٧ بيكومول/لتر لدى المصابين بالرخد وكان أقل بكثير من مثيله لدى الأطفال الأسوياء. لم يظهر أي اختلاف يذكر في مستوى الأنسولين بحالة الصيام أو غيره بعد تسريب الأرجنين عما كان عليه لدى أطفال المجموعة الضابطة. ولم تكن هناك اختلافات ذات أهمية في مستويات هورمون النمو بحالة الصيام أو المستحث بالأرجنين بين المصابين بالرخد والأسوياء. كما لم تختلف تركيزات عامل النمو I و II الشبيه بالأنسولين بين المجموعتين. تشير هذه البيانات إلى غياب أي دور رئيس لهورمون النمو الجائل (وسوماتويدين ضمنيًّا) في تمعدن العظام.

We evaluated arginine-induced insulin and growth hormone secretion in 10 children with proved vitamin-D-deficiency rickets and compared these values with those of eight normal age-matched control children. Thirty minutes after an intravenous infusion of arginine hydrochloride (10% solution, 0.5 g/kg), the mean serum insulin level was 159.3 ± 122.7 pmol/L for the rachitic children, which was significantly lower than that for the normal children. Neither the fasting insulin level nor any others after the arginine infusion differed significantly from those for the control children. There were no significant differences in the fasting or the arginine-stimulated growth hormone levels between the rachitic and control children. The concentrations of insulinlike growth factor I and II did not differ between the two groups. These data suggest that there is not a major role for circulating growth hormone (and by implication somatomedin) on bone mineralization.

Vitamin D is essential for calcium and phosphorus homeostasis in higher animals.[1] This process is regulated by an endocrine system that coordinates the sequential metabolism of vitamin D_3 into its two principal biologically active metabolites, 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3.[1-3] The best documented biological actions of vitamin D_3 and of its most active metabolite, 1,25$(OH)_2D_3$, are the stimulation of intestinal calcium absorption and the mobilization of bone calcium.[1]

A vitamin-D-dependent calcium-binding protein previously found in the intestines of chicks and of humans has been discovered in pancreatic tissue.[4-6] This finding may imply a link between vitamin D_3 levels and insulin secretion. Recent autoradiographic studies have shown that the beta cells of the islets can concentrate 1,25$(OH)_2D_3$ in their nuclei and suggest a genomic action of B cell function.[6,7] Glucose tolerance is impaired in vitamin-D-deficiency states,[8,10] and a number of investigators have suggested a direct link between levels of serum calcium and vitamin D on the one hand and insulin secretion on the other.[11-13]

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In addition several investigators have linked pituitary hormone secretion with calcium and vitamin D status; for example, growth hormone (GH) secretion affects intestinal calcium absorption as well as bone mineral homeostasis.[14-21]

To determine the effect of vitamin D deficiency on insulin and GH secretion, we performed arginine infusion tests on 10 children with proved nutritional rickets and eight normal age-matched control children.

Patients and Methods

Ten Egyptian children with vitamin-D-deficiency rickets as diagnosed by clinical, laboratory, and radiologic criteria were the subjects of this study. Eight age-matched normal children served as controls. The studies were carried out on the nutritional ward of Alexandria University Children's Hospital. Informed consent was obtained from the parents of each child.

All the children had a complete history including the following: careful questioning concerning nutritional intake; a thorough physical examination with emphasis on rachitic signs, including hypotonia, broadening of epiphysis, craniotabes, bossing of the skull, wide anterior fontanel, costochondral beading, delayed developmental milestones, and deformities and/or fractures; plain x-rays of the wrists; and laboratory investigations including serum calcium, phosphorus and alkaline phosphotase, urea nitrogen, and albumin concentrations.

After an 8-hour overnight fast, blood samples were withdrawn through a polyethylene catheter inserted in a forearm vein. An intravenous arginine hydrochloride infusion (10% solution, 0.5 g/kg) was begun and continued for 30 minutes. Blood samples were obtained before and 30, 60, 75, and 90 minutes after the beginning of the infusion. The serum was separated from the formed elements by centrifugation and kept frozen at –20°C until analyzed for GH,[22] insulinlike growth factor (IGF) I[23] and II,[24] and insulin[25] concentrations by standard double antibody radioimmunoassays. The intra-assay coefficient of variation averaged 8% in the range of insulin values detected and 7% in the range of GH concentrations measured. For IGF-I and IGF-II these were less than 13% and 9%, respectively. All the rachitic children improved markedly in response to a single dose of vitamin D, 600,000 units intramuscularly, as evidenced by disappearance of signs of active rickets and healing of their bones radiologically as well as by return of serum phosphorus and alkaline phosphatase to normal values. Statistical analysis was performed by the unpaired Student *t* test. Statistical significance was considered $P < 0.05$.

Results

The biochemical criteria for the diagnosis of rickets are an elevated alkaline phosphatase level, decreased calcium × phosphate product (Ca × PO_4), and usually diminished circulating total calcium and phosphate concentrations. These data as well as the basal urea nitrogen and albumin concentrations and the IGF-I and IGF-II are presented in Table 1. The mean (± SD) serum calcium concentration was 2.2 ± 0.12 mmol/L for the rachitic children and 2.5 ± 0.08 mmol/L for the control children ($P < 0.001$). The serum phosphate levels were also significantly lower in rachitic children (1.0 ± 0.09 mmol/L) versus 1.6 ± 0.05 mmol/L for the control children ($P < 0.001$). Thus, the Ca × PO_4 product was much lower in the rachitic children (2.2 ± 0.2) versus 4.0 ± 0.2 for the controls ($P < 0.001$). The alkaline phosphatase levels were markedly raised in the rachitic children (169.0 ± 20.0 U/L versus 66.7 ± 21.3 U/L for the control children) ($P = 0.001$). There was no evidence for renal failure in either group (urea nitrogen = 5.4 ± 0.8 mmol/L of urea for the rachitic children versus 5.1 ± 0.5 mmol/L of urea for the controls). Serum albumin concentrations were marginally higher in the rachitic children (38 ± 8 g/L) versus 31 ± 5 g/L in the controls ($P = 0.046$).

The GH, insulin, and glucose responses to the arginine infusion as well as the I:G ratios are shown in Table 2. In the rachitic children, the mean insulin level (159.3 ± 122.7 pmol/L) and the insulin:glucose (I:G) ratio (30.1 ± 22.2), 30 minutes after the start of the arginine infusion, were significantly below those of the control children (454.9 ± 277.7 pmol/L and 103.4 ± 71.1) ($P = 0.004$ and 0.001, respectively). Neither the fasting insulin level nor any others after the arginine infusion differed significantly from those of the control children.

TABLE 1. *Biochemical data in rachitic and control children.*

	Age (mo)	Weight (%)	Ca (mmol/L)	PO_4 (mmol/L)	Ca × PO_4 product	Alk phos (U/L)	Urea (mmol/L)	Alb (g/L)	IGF-I (U/mL)	IGF-II (μg/L)
Rachitic children										
1	15.5	98	2.4	1.0	2.4	142.0	5.4	44	0.42	218
2	9.5	103	2.0	1.0	2.0	156.2	4.3	46	0.22	188
3	13.5	89	2.2	0.9	2.0	177.5	6.4	42	0.18	197
4	11	91	2.1	1.0	2.1	163.3	5.4	24	0.09	162
5	10	115	2.1	1.2	2.5	170.4	5.4	41	0.17	116
6	20	100	2.3	1.0	2.3	177.5	5.7	39	0.21	111
7	9	95	2.3	0.9	2.1	163.3	6.4	44	0.16	270
8	12	111	2.0	1.0	2.0	177.5	5.0	37	0.17	262
9	18	104	2.2	0.9	2.0	213.0	3.9	25	0.15	166
10	11	106	2.0	1.0	2.0	149.1	6.1	36	0.12	165
Mean	13	101	2.2	1.0	2.2	169.0	5.4	38	0.19	186
SD	3.8	8.4	0.12	0.09	0.2	20.0	0.8	8	±0.09	±54
Control children										
1	6	119	2.4	1.6	3.8	63.9	5.7	31	0.12	171
2	9	101	2.5	1.6	4.0	78.1	5.4	34	0.22	183
3	9	103	2.5	1.5	3.7	99.4	4.3	25	0.28	247
4	18	103	2.4	1.6	3.8	71.0	5.4	33	0.09	139
5	10.5	118	2.6	1.6	4.2	85.2	5.0	34	0.32	149
6	10	92	2.6	1.5	3.9	42.6	5.4	34	0.10	271
7	7	114	2.4	1.6	3.8	56.8	4.3	37	0.12	276
8	20	105	2.5	1.5	3.7	35.5	5.4	23	0.33	356
Mean	11.2	107	2.5	1.6	4.0	66.7	5.1	31	0.20	356
SD	5.1	9.3	0.08	0.05	0.2	21.3	0.5	5	±0.10	±76
P value	0.426	0.21	<0.001	<0.001	<0.001	0.001	0.361	0.046	1.000	0.316

TABLE 2. *GH, insulin, and glucose responses to arginine infusion.*

	Fasting	30-min	60-min	75-min	90-min
Rachitic children					
GH (μg/L)	6.0 ± 5.1	10.2 ± 6.8	15.6 ± 13.0	10.1 ± 10.8	9.3 ± 10.9
Insulin (pmol/L)	63.8 ± 54.5	159.3* ± 122.7	114.1 ± 94.7	106.9 ± 96.1	102.6 ± 111.9
Glucose (mmol/L)	4.1 ± 0.5	5.3 ± 1.3	4.7 ± 0.7	4.6 ± 0.5	4.6 ± 0.6
I:G ratio	0.16 ± 0.14	0.30* ± 0.22	0.24 ± 0.20	0.23 ± 0.21	0.22 ± 0.24
Control children					
GH (μg/L)	5.9 ± 2.3	11.6 ± 4.8	14.3 ± 5.4	10.8 ± 5.9	8.4 ± 6.0
Insulin (pmol/L)	94.7 ± 74.6	454.9 ± 277.8	130.6 ± 87.5	78.2 ± 37.3	68.9 ± 32.3
Glucose (mmol/L)	3.6 ± 0.2	4.4 ± 0.3	4.6 ± 0.6	4.5 ± 0.7	4.4 ± 0.8
I:G ratio	0.27 ± 0.22	103.0 ± 0.71	0.28 ± 0.20	0.17 ± 0.07	0.16 ± 0.07

*$P < 0.01$ when the rachitic group was compared to control group.

There were no significant differences in the fasting or the arginine-stimulated GH levels between the rachitic and control groups (Table 2). The IGF-I and IGF-II levels did not differ between the rachitic and normal children (Table 1).

Discussion

Our data show a marked deficit in insulin secretion at the end of a 30-minute infusion of arginine hydrochloride in children with vitamin-D-deficiency rickets compared to normal children. At all other times, the insulin levels were indistinguishable between the two groups of children. These findings support previous studies on experimental animals in demonstrating that vitamin D deficiency can lead to impaired insulin secretion.[8,11] Hypocalcemia is unlikely as a cause of this observed impairment in our vitamin-D-deficient children since calcium infusion into vitamin-D-deficient, hypocalcemic rats did not improve insulin secretion, whereas vitamin D repletion markedly improved it.[8,11,12,26] The demonstrated impairment of the first phase of insulin secretion, which is primarily dependent on the handling of intracellular calcium,[27] suggests that vitamin D deficiency may alter the pancreatic B cell levels of stored calcium. This may be mediated through the pancreatic vitamin-D-dependent calcium-binding protein recently demonstrated in experimental animals.[28]

The demonstration of target cells for $1,25(OH)_2D_3$ in the anterior pituitary[14] may imply a role for vitamin D in anterior pituitary hormone secretion as it does with insulin. However, our finding of normal GH responses to arginine in the vitamin-D-deficient children does not support a major role, at least for GH secretion.

Growth hormone has been suggested to be an important regulator of bone growth and mineralization, either directly or indirectly through somatomedin.[5,16,29,30] Moreover, it is proposed that GH can maintain the Ca × PO_4 product at a suitable high level through its various effects on vitamin D metabolism,[16,18,31-35] parathyroid hormone,[36] and intestinal calcium absorption.[37]

However, the basal GH levels as well as the IGF I and II concentrations were normal in the vitamin-D-deficient children despite their demineralized bones, and low Ca × PO_4 products. These data suggest that circulating GH and IGF-I and IGF-II do not play an important role in bone mineral homeostasis in children with nutritional rickets.

References

1. Norman AW. Vitamin D: the calcium homeostatic steroid hormone. New York: Academic Press, 1979.
2. Haussler MR, McCain TA. Basic and clinical concepts related to vitamin D metabolism and action (second of two parts). N Engl J Med 1977;297(19):1041-50.
3. Henry HL, Norman AW, Malluche H. 24R,25 dihydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 are both indispensible for calcium and phosphorus homeostasis. Life Sci 1978;201:825.
4. Christakos S, Norman AW. Studies on the mode of action of calciferol XVIII: evidence for a specific high affinity binding protein for 1,25 dihydroxyvitamin D_3 in chick kidney and pancreas. Biochem Biophys Res Commun 1979;89(1):56-63.
5. Arnold BM, Kuttner M, Willis DM, et al. Radioimmunoassay studies of intestinal calcium-binding protein in the pig: II. The distribution of intestinal CaBP in pig tissues. Pharmacol 1975;53(6):1135-40.
6. Clark SA, Stumpf WE, Sar M, et al. Target cells for 1,25 dihydroxyvitamin D_3 in the pancreas. Cell Tissue Res 1980;209(3):515-20.
7. Sar M, Stumpf WE. Combined autoradiography and immunohistochemistry for simultaneous localization of radioactivity labeled steroid hormones and antibodies in the brain. J Histochem Cytochem 1981;29(1A suppl):161-6.
8. Nyomba BL, Bouillon R, De Moor P. Influence of vitamin D status on insulin secretion and glucose tolerance in the rabbit. Endocrinology 1984;115(1):191-7.
9. Curry DL, Bennett LL, Grodsky GM. Dynamics of insulin secretion by the perfused rat pancreas. Endocrinology 1968;83:572-84.
10. Rayssiquier Y, Chevalier F, Gueux E, et al. Glucose-stimulated insulin secretion in rats with normal plasma calcium levels: effects of calcium deficiency. J Nutr 1982;112(9):1801-4.
11. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. Science 1980:209(4458):823-5.
12. Clark SA, Stumpf WE, Sar M. Effect on 1,25 dihydroxyvitamin D_3 on insulin secretion. Diabetes 1981;30(5):382-6.
13. Frazer TE, White NH, Hough S, et al. Alterations in circulating vitamin D metabolites in the young insulin-dependent diabetic. J Clin Endocrinol Metab 1981;53(6):1154-9.
14. Narbaitz R, Stumpf WE, DeLuca HF. Thyrotropes in the pituitary are target cells for 1,25 $(OH)_2$ vitamin D. Cell Tissue Res 1980;209:161-6.
15. Stumpf WE, Sar M, Reid FA, et al. Target cells for 1,25-dihydroxyvitamin D_3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid. Science 1979;206(4423):1188-90.
16. Krabbe S, Transbol I, Christiansen C. Bone mineral homeostasis, bone growth and mineralization during years of pubertal growth: a unifying concept. Arch Dis Child 1982;57(5):359-63.

17. Krabbe S, Christiansen C, Rodbro P, Transbol I. Effects of puberty on rates of bone growth and mineralisation with observations in male delayed puberty. Arch Dis Child 1979;54(12):950-3.
18. Gray RW, Garthwaite TL, Phillips LS. Growth hormone and triiodothyronine permit an increase in plasma 1,25 $(OH)_2D_3$ concentrations in response to dietary phosphate deprivation in hypophysectomized rats. Calcif Tissue Int 1983;35(1):100-6.
19. Yeh JK, Aloia JF. Effect of hypophysectomy and 1, 25-dihydroxyvitamin D on duodenal calcium absorption. Endocrinology 1984;114(5):1711-7.
20. Spanos E, Barrett D, MacIntyre I, et al. Effect of growth hormone on vitamin D metabolism. Nature 1978;273(5659):246-7.
21. Bruns MEH, Vollmer SS, Bruns DE. Human growth hormone increases intestinal vitamin D dependent calcium-binding protein in hypophysectomized rats. Endocrinology 1983;113(4):1387-92.
22. Odell WD. Growth hormone. In: Nichols AL, Nelson JC, eds. Application in radioimmunoassay manual. Nichols Institute, 1977;237.
23. Copeland KC, Underwood LE, Van Wyk JJ. Induction of immunoreactive somatomedin C human serum by growth hormone: dose-response relationships and effect on chromatographic profiles. J Clin Endocrinol Metab 1980;50(4):690-7.
24. Hintz RL, Liu F. A radioimmunoassay for insulin-like growth factor II specific for the C-peptide region. J Clin Endocrinol Metab 1980;54(2):442-6.
25. Freedlander AE, Vandenhoff GE, Malcolm RR. Radioimmunoassay of insulin. In: Larner J, Pohl SL, eds. Methods in diabetes research, vol 1. New York: Wiley Interscience, 1984;295.
26. Kadowaki S, Norman AW. Dietary vitamin D is essential for normal insulin secretion from the perfused rat pancreas. J Clin Invest 1984;73(3):759-66.
27. Kikuchi M, Wollheim CB, Siegel EG, et al. Biphasic insulin release in rat islets of Langerhans and the role of intracellular Ca++ stores. Endocrinology 1979;105(4):1013-9.
28. Kadowaki S, Norman AW. Pancreatic vitamin D-dependent calcium binding protein: biochemical properties and response to vitamin D. Arch Biochem Biophys 1984;233(1):228-36.
29. Thorngren KG, Hansson LI. Stimulation of longitudinal bone growth by hypophyseal hormones in the hypophysectomized rat. Acta Endocrinol 1977;84(3):485-96.
30. Kawai K, Ogata E. The role of Ca++ in sulfation factor activity on embryonic chick cartilage. Metabolism 1981;30(8):761-4.
31. Brown DJ, Spanos E, MacIntyre I. Role of pituitary hormones in regulating renal vitamin D metabolism in man. Br Med J 1980;280(6210):277-8.
32. Burstein S, Chen IW, Tsang RC. Effects of growth hormone replacement therapy on 1,25 dihydroxyvitamin D and calcium metabolism. J Clin Endocrinol Metab 1983;56(6):1246-51.
33. Gray RS. Control of plasma 1,25 dihydroxyvitamin vitamin D concentrations by calcium and phosphorus in the rat effects of hypophysectomy. Calcif Tissue Int 1981;33:458.
34. Pahuja DN, DeLuca HF. Role of the hypophysis in the regulation of vitamin D metabolism. Mol Cell Endocrinol 1981;23(3):345-50.
35. Spencer EM, Tobiassen O. The mechanism of the action of growth hormone on vitamin D metabolism in the rat. Endocrinology 1981;108(3):1064-70.
36. Lancer SR, Bowser EN, Hargis GK. The effect of growth hormone on parathyroid function in rats. Endocrinology 1976;98(5):1289-93.
37. Yeh JK, Aloia JF. Effect of hypophysectomy and 1,25-dihydroxyvitamin D on duodenal calcium absorption. Endocrinology 1984;114(5):1711-7.

SCALP FUNGUS INFECTIONS IN THE EASTERN PROVINCE OF SAUDI ARABIA

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تم فحص خمسمائة وخمسين مريضا يافعا لاحتمال إصابتهم بسعفة الرأس وذلك خلال الفترة ما بين شهري نيسان / ابريل ١٩٨٤م وآذار / مارس ٩٨٧م شكّل المرضى السعوديون ٨٤٪ منهم. أُكد التشخيص السريري بالفحص المجهري لدى ٥٠٧ حالات (٩٢ر٢٪) وبالزرع لدى ٤٤٢ حالة (٤٤٧ معزولة). كانت البويغاء الكلبية العامل الأكثر تواترا في سعفة الرأس حيث سببت إصابة ٢٥٣ حالة (٥٦ر٦٪ من ٤٤٧ معزولة)، تلتها الفطور الشعرية المتفرعة (١٣٧ حالة أو ٣٠ر٦٪) فالبويغاء الأدوينية (٣٨ أو ٨ر٥٪) ففطور سعفة الذقن (١٨ أو ٤٪) وأخيرا البويغاء الحديدية (حالة واحدة أو ٠ر٢٪). ونجحت المعالجة بالغريزيو فلفين، عن طريق الفم (١٠ الى ١٥ مغم/كغم/يوميا) لمدة شهرين إلى ثلاثة أشهر مع ايميدازول موضعي، في جميع الحالات الايجابية. وأما حالات الشهدة فقد تطلبت إلى جانب الغريزيوفلفين بنسلين عن طريق الفم.

Five hundred fifty prepubescent suspected cases of tinea capitis were examined during the period April 1984 to March 1987. Saudi patients comprised 84.0% of the examined cases. The clinical diagnosis was confirmed by microscopic examination in 507 cases (92.2%) and by culture in 442 cases (447 isolates). *Microsporum canis* was the commonest agent of tinea capitis, causing 253 infections (56.6% of the 447 isolates). Next in frequency were *Trichophyton violaceum* (137 or 30.6%), *M. audouinii* (38 or 8.5%), *T. mentagrophytes* (18 or 4.0%), and *M. ferrugineum* (1 or 0.2%). Treatment with oral griseofulvin (10 to 15 mg/kg/day) for 2 to 3 months combined with a topical imidazole agent (clotrimazole or miconazole) was effective in all positive cases. Patients with kerion required treatment with oral penicillin in addition to griseofulvin.

Although tinea capitis occurs frequently in the Eastern Province of Saudi Arabia, there have been only two studies available about these infections. One was a preliminary report of 39 scalp infections among 143 patients with suspected dermatophytic infections.[1] The second was a study by the present authors of 450 suspected scalp fungus infections from a total of 723 children with suspected dermatomycosis.[2]

The present survey was made to assess the status of this disease and to identify the causative fungi.

Materials and Methods

Five hundred fifty clinically suspected cases of scalp fungus infections were examined. Standard methods were followed for specimen collection, culture, and identification of the isolated pathogens.[3] For microscopic examination, part of the material (hair, pus, or scales) from the affected site was examined in potassium hydroxide-dimethyl sulfoxide mount (60 mL distilled water, 20 g potassium hydroxide, and 40 mL dimethyl sulfoxide).

Proved cases of tinea capitis were treated with oral griseofulvin (10 to 15 mg/kg/day) and topical

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application of an imidazole agent for a period of 2 to 3 months. For kerion cases, potassium permanganate solution (dilution 1:1000) was used for cleaning the area, and treatment consisted of oral penicillin in addition to griseofulvin.

Results

Of 550 clinically suspected cases of tinea capitis, 286 (52.0%) occurred in males and 264 (48.0%) in females. All patients were between the ages of 10 months and 12 years from 12 nationalities. Saudis comprised the largest group of 463 (84.1%). These cases showed three clinical types of scalp fungus infections: scaly, inflammatory, and black-dot types (Figures 1 through 6). Fifteen patients had kerion as well.

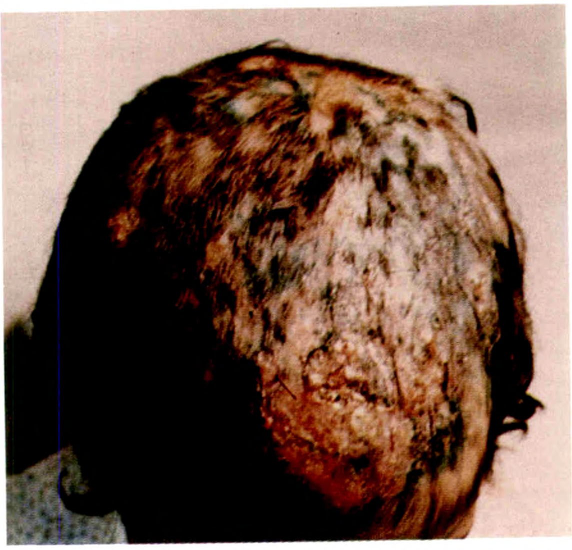

FIGURE 1. Kerion. Acute inflammatory reaction to scalp infection with *M. canis* in a 7-year-old girl.

On direct microscopy 507 cases (92.2%) were positive. Fifteen cases with kerion showed small spores (2 to 3 μ) occurring in masses on the surface of the hair shafts, which was highly characteristic for fungal infection (*M. canis*). Of the 507 positive cases, 442 (87.2%) were positive on culture. In five instances double isolations were obtained from the same clinical specimen. These combinations were *Microsporum canis* and *Trichophyton violaceum* in three; *M. canis* and *T. mentagrophytes* in one; and *M. audouinii* and *T. violaceum* in one. *Microsporum canis* was identified

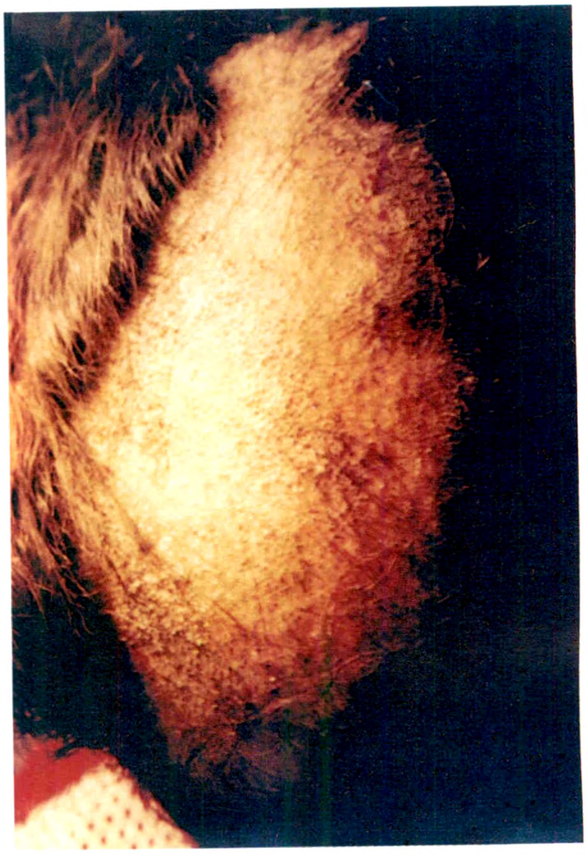

FIGURE 2. Black-dot appearance of tinea capitis caused by *T. violaceum* within big areas of hair loss in a 9-year-old girl.

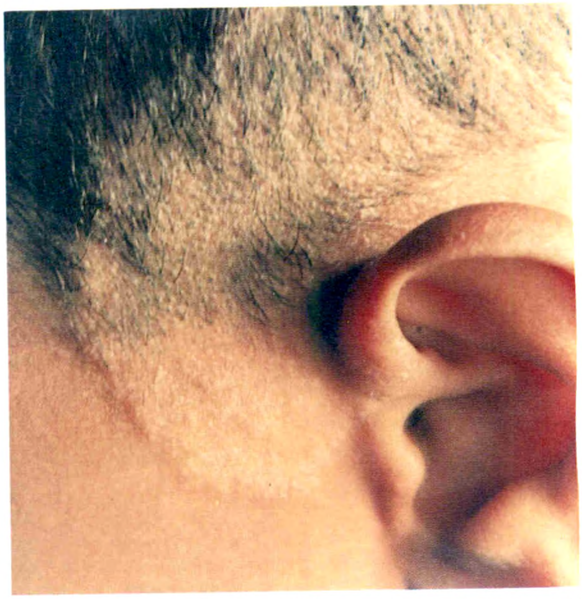

FIGURE 3. A 6-year-old boy with black-dot tinea capitis caused by *T. violaceum* with a lesion of papular border involving the scalp and skin around the left ear.

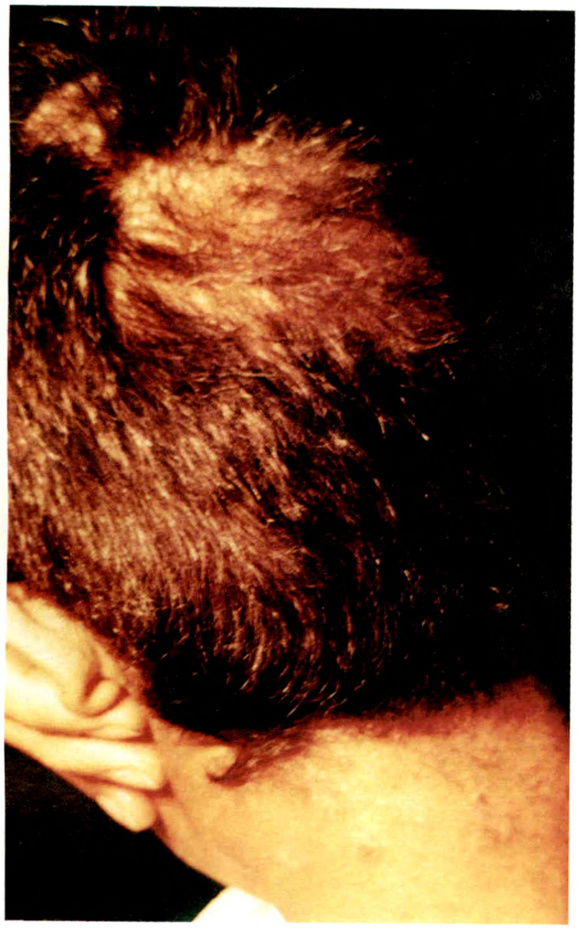

FIGURE 4. *T. violaceum* tinea capitis with papular border and scaly surface extending down to the neck in a 6-year-old boy.

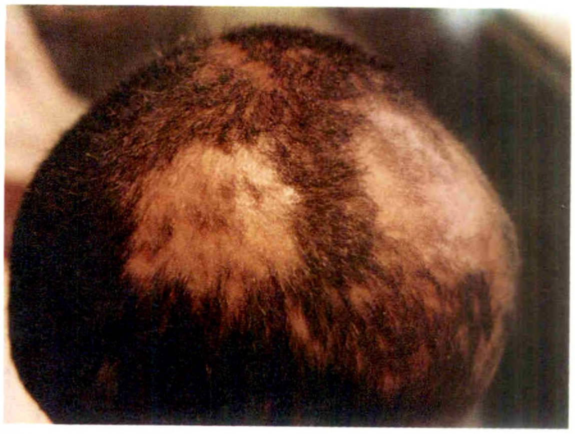

FIGURE 5. *M. canis* tinea capitis with widespread areas of fine, white adherent scales and diffuse hair loss in a 8-year-old boy.

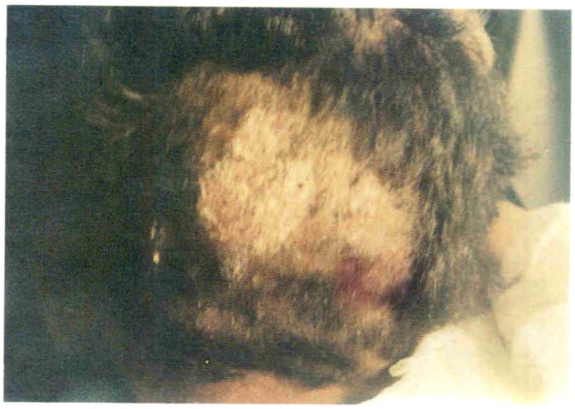

FIGURE 6. *M. audouinii* tinea capitis in a 2-year-old boy.

in 253 isolates (56.6%), *T. violaceum* in 137 (30.7%), *M. audouinii* in 38 (8.5%), *T. mentagrophytes* in 18 (4.0%), and *M. ferrugineum* in one (0.2%).

Griseofulvin therapy with topical application of an imidazole agent (clotrimazole or miconazole) in noninflammatory cases and combined with systemic antibiotic (oral penicillin) in kerion cases gave satisfactory results in all our patients. No resistance to treatment was observed.

Discussion

Of the 550 patients included in this study 507 (92.2%) had their diagnosis confirmed by direct microscopy and in 442 of them (87.2%) the causative organism was determined.

Microsporum canis was the most common etiologic agent (253 or 56.6% of the 447 isolates). Next in frequency were *T. violaceum*, *M. audouinii*, *T. mentagrophytes*, and *M. ferrugineum*. *Trichophyton schoenleini* was conspicuous by its absence in this area of the Kingdom, while in neighboring Iraq, favus was the most common disease observed by Rahim in 1966[4] who reported that no *Microsporum* or other zoophilic dermatophytes were observed to cause ringworm of the scalp in Iraq. *Microsporum canis*, the commonest isolate from scalp infections, has been reported by Kolemen et al[1] from the Eastern Province. However, *T. violaceum* was the commonest isolate reported in Egypt,[5,6] Libya,[7,8] and India.[9,10] *Trichophyton verrucosum* was the commonest isolate in Ankara, Turkey.[11] Reports from the United States cited *M. audouinii* and *T. tonsurans* as common isolates.[12-15] In Western Australia, *M. canis* occurred most commonly.[16] Table 1 summarizes and compares these different regional findings.

TABLE 1. *Epidemiology of tinea capitis infection in Eastern Province of Saudi Arabia and other countries.*

Reference	Percentage of fungal isolates											
	M. canis	*M. audouinii*	*M. gypseum*	*M. ferrugenium*	*M. nanum*	*T. violaceum*	*T. mentagrophytes*	*T. verrucosum*	*T. schoenleini*	*T. tonsurans*	*T. rubrum*	*T. simi*
Present study, Eastern Province	56.6	8.5	–	0.2	–	30.7	4.0	–	–	–	–	–
Rahim, Iraq[4]	–	–	–	–	–	–	–	–	100.0	–	–	–
El-Mofty et al, Egypt[5]	12.0	–	–	–	3.2	66.4	4.0	–	14.4	–	–	–
Abdel Fattah and Al-Gothamy, Egypt[6]	18.0	–	–	–	–	53.0	–	–	26.7	–	–	–
Bhakhtavizian et al, Tripoli, Libya[7]	20.0	–	–	–	–	60.7	1.1	–	4.8	5.7	–	–
Malhotra et al, Benghazi, Libya[8]	–	23.8	–	–	–	–	–	–	69.5	–	–	–
Koleman, Ankara, Turkey[11]	13.9	5.5	2.8	–	–	13.9	11.1	36.1	11.1	5.6	–	–
Kamalam and Thambiah, Madras, India[10]	–	–	–	–	–	73.94	3.08	–	–	13.16	8.4	1.4
Khosa et al, Varanasi, India[9]	–	–	–	1.89	–	54.72	7.55	3.77	22.65	–	9.43	–
Terreni, Charleston, USA[12]	2.9	96.7	–	–	–	–	–	–	–	0.4	–	–
Adams and Riley, Charleston, USA[13]	39.0	50.0	5.0	–	–	–	–	–	–	5.0	–	–
Prevost et al, Charleston, USA[14]	–	9.4	–	–	–	–	–	–	–	90.6	–	–
Rose, Western Australia[16]	90.8	–	–	–	–	–	–	–	–	–	–	–

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References

1. Kolemen F, Abdel Gawad A, Anter S, Kubba R. Dermatophytic flora of the Eastern Province in Saudi Arabia. King Faisal Specialist Hosp Med J 1984;4(4):313-6.
2. Al-Sogair SM, Al-Humaidan YM, Moawad MK. Superficial mycotic skin infections in Eastern Province of Saudi Arabia. Presented at XVII World Congress of Dermatology, Berlin, 24-29 May 1987.
3. Ajello L, George LK, Kaplan W, Kaufman L. Laboratory manual for medical mycology, publication No. 994. Washington: US Government Printing Office, 1963.
4. Rahim GF. A survey of fungi causing tinea capitis in Iraq. Br J Dermatol 1966;78(4):213.
5. El-Mofty A, Mostafa AM, Mohareb RW, et al. Scalp fungus infections in Egypt. Mansoura Med Bull 1975;3(3-4):331-6.
6. Abdel-Fattah A, Al-Gothamy Z. Tinea capitis in Egypt. Mykosen 1967;10(5):189-94.
7. Bhakhtavizian C, Shafi M, Mehta M, et al. Tinea capitis in Tripoli. Clin Exp Dermatol 1984;9:84-8.
8. Malhotra YK, Garg MP, Kanwar AJ, Nagrajan S. A study of tinea capitis in Libya (Benghazi). Sabouraudia 1979;17:181-3.
9. Khosa RK, Girgla HS, Hajini GH, et al. Study of dermatomycoses. Int J Dermatol 1981;20(2):130-2.
10. Kamalam A, Thambiah AS. Tinea capitis: an endemic disease in Madras. Mycopathologia 1980;71(1):45-51.
11. Kolemen F. Dermatophytic flora of Ankara (Turkey). Dermatologica 1981;162(4):260-4.
12. Terreni AA. Tinea capitis survey in Charleston, SC. Arch Dermatol 1961;83:88-91.
13. Adams A, Riley K. Tinea capitis: a report of 100 cases. J SC Med Assoc 1954;50:6-7.
14. Prevost E. Nonfluorescent tinea capitis in Charleston, SC: a diagnostic problem. JAMA 1979;242(16):1765-7.
15. Krowchuk DP, Lucky AW, Primmer SI, McGuire J. Current status of the identification and management of tinea capitis. Pediatrics 1983;72(5):625-31.
16. Rose M. Fungal infections of the scalp in Western Australia. Sabouraudia 1980;18(3):185-90.

GLUTATHIONE REDUCTASE DEFICIENCY IN SAUDI ARABIA

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استقصي عوز الأنظيم المرجع للغلوتاتيون في كريات الدم الحمراء لدى سكان المنطقة الوسطى بالمملكة العربية السعودية باستخدام مقياس الضوء الطبقي لتقدير الأنظيم في وجود فلافين أدينين ثنائي النوويد وغيابه. وقد تم تحليل عينات دم من ٣٧٤ ذكرًا و ٢١١ أنثى ووجد أن تواتر العوز الجزئي للأنظيم كان ٠ر٠٥٣ و٠ر٠٥٢ لدى جمهرة الذكور والإناث على التوالي. كما تم تحديد حالات من عوز الأنظيم مرتبطة بالتلاسيمية وتبين أن القيم الدموية كانت متأثرة بهذا الارتباط.

Erythrocyte glutathione reductase (GR) deficiency was investigated in the population of the Central Province of Saudi Arabia using spectrophotometric estimation of GR in the presence and absence of flavin adenine dinucleotide. Blood samples from 374 males and 211 females were analyzed, and the frequency of partial GR deficiency was found to be 0.053 and 0.052 in the male and female populations, respectively. Cases of GR deficiency associated with α-thalassemia were identified, and hematologic values were shown to be influenced in this association.

Glutathione reductase (GR) plays an essential role in maintaining the stability of red cell membrane proteins and hemoglobin by catalyzing the conversion of oxidized glutathione (GSSG) to reduced glutathione using either NADPH or NADH as a coenzyme. Reduced glutathione is a tripeptide with a free -SH group and protects red blood cells against oxidative attacks of various oxidizing metabolites and drugs. The extent of conversion of oxidized glutathione to its reduced form depends on normal functioning of GR. Several clinical conditions have been described in which the GR activity may be abnormal. These include hemophilia B, leukemia,[1] α-thalassemia,[2] and homozygous Hb C disease.[3] The dietary riboflavin level plays an important role, and in several studies riboflavin deficiency has been shown to be associated with reduced GR activity.[4,5]

In an earlier study, we investigated the frequency of GR deficiency in two provinces of Saudi Arabia where the frequency of sickle cell, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency genes was high and encountered several cases with partial GR deficiency.[6] We extended our investigations to the population of Riyadh in the Central Province where the frequency of red cell genetic disorders is considerably lower.[7,8] This paper reports the frequency of GR deficiency in Saudi males and females in Riyadh and presents the hematologic values in patients with GR deficiency. The results obtained in the population of Riyadh are compared with those obtained in other regions of Saudi Arabia.

Materials and Methods

Blood samples were collected from male and female Saudi blood donors and individuals attending the outpatient clinics of King Khalid University Hospital, Riyadh. Five milliliters of blood were collected by venipuncture in heparinized tubes. Hematologic values were determined using a Coulter counter ZF6 with hemoglobinometer attachment. Red cell indices were obtained from

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Coulter counter ZF6 or were calculated using standardized procedures.[9]

The cells were separated from the plasma by centrifugation, washed twice with cold saline, and hemolyzed. The hemolysate was subjected to electrophoresis at alkaline pH on agarose film using 0.05M sodium barbital, pH 8.6[10] to determine the presence of abnormal hemoglobins. The Hb A_2 and Hb F levels were estimated using an elution method following cellulose acetate electrophoresis[10] and alkali denaturation,[11] respectively.

The activity of GR was determined spectrophotometrically using the method described by Beutler.[12] The decrease in absorbance was followed at 340 nm in a test system containing 0.1M tris-HCl buffer, pH 8.0, 0.05M EDTA, 2 mM NADPH, and 1 mM GSSG, in both the presence and absence of flavin adenine dinucleotide (FAD).

The G6PD activity was estimated in hemolysate using kits from Boehringer Mannheim.

The cases with GR deficiency were separated, and the hematologic values were analyzed; the mean and standard deviation were obtained for each value, and the range was calculated as mean ± 2SD.

Results

Samples were screened from 374 male subjects and 211 female subjects. The activity of GR in the presence and absence of FAD was used to calculate the activity coefficient (AC) as follows: AC = GR unit in the presence of FAD/GR unit in the absence of FAD. The normal range of AC was taken as 0.9 to 1.2.[13] Samples showing an increase in GR activity in the presence of FAD had AC values above 1.3, suggestive of riboflavin deficiency (such samples were not considered GR deficient). Only those samples which had low GR activity in the presence and absence of FAD were regarded as GR deficient. No case of complete GR deficiency was encountered. Partial GR deficiency was found in both the male and female populations at a frequency of 0.053 and 0.052, respectively (Table 1).

TABLE 1. *Frequency of partial GR deficiency in different areas of Saudi Arabia.*

Area investigated	Province of Saudi Arabia	Frequency of partial GR deficiency	
		Male	Female
Khaibar[6]	Northwestern	0.096	0.049
Hofuf[6]	Eastern	0.150	0.143
Riyadh (present study)	Central	0.053	0.052

The hematologic values in patients with partial GR deficiency are presented in Table 2. In the majority of the GR-deficient cases, GR activity was less than 50% of normal for this population. Only one female had less than 20% of normal GR activity and mild anemia. In the majority of other females, slightly lower hematologic values were obtained. Three of the females had associated α-thalassemia with reduced values of red cell indices: mean cell volume (MCV), mean cell hemo-

TABLE 2. *Mean hematologic values in nonthalassemic, partially GR-deficient Saudi males and females in Riyadh.*

	No. investigated	Hematologic values (mean ± SD)							
		RBC ($\times 10^{12}$/L)	Hb (mmol/L)	PCV (L/L)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	Hb A_2 (%)	Hb F (%)
GR deficient									
Male	17	5.01 ± 0.54	9.74 ± 0.49	0.38 ± 0.03	84.00 ± 2.50	1.93 ± 0.21	25.50 ± 1.88	3.00 ± 0.23	0.55 ± 0.25
Female	8	4.40 ± 0.53	7.88 ± 0.61	0.38 ± 0.04	87.60 ± 4.00	1.81 ± 0.09	20.85 ± 0.62	3.10 ± 0.25	0.50 ± 0.25
Normal									
Male	354	5.70 ± 0.44	9.55 ± 0.74	0.44 ± 0.05	84.20 ± 2.50	1.76 ± 0.09	20.47 ± 0.62	3.00 ± 0.30	0.60 ± 0.25
Female	200	4.90 ± 0.44	8.44 ± 0.68	0.40 ± 0.03	84.20 ± 2.50	1.76 ± 0.09	20.54 ± 0.62	3.00 ± 0.25	0.55 ± 0.22

globin (MCH), and mean cell hemoglobin concentration (MCHC). In addition, all these patients were slightly anemic. In the male group, only one subject had anemic presentation who also had associated α-thalassemia, and this lowered the MCV, MCH, and MCHC severely. Two other male patients with α-thalassemia were identified. The hematologic values in thalassemic and nonthalassemic GR-deficient individuals are presented in Table 3.

In the Riyadh population, the frequency of G6PD deficiency in males was 0.039. None of the cases had associated G6PD and GR deficiency. Among females, the G6PD deficiency was not determined due to the inability to recognize heterozygotes by the method used in this study. No association could be seen between GR deficiency and the sickle cell gene (Hb S) due to the low frequency of the Hb S gene in the Riyadh area.

Discussion

Glutathione reductase deficiency is regarded as a common disorder in several populations, though it is suggested that reduced GR activity due to riboflavin deficiency is more common compared to deficiency due to genetically determined variants.[14] In several sporadic cases, with hemolytic anemia resulting from ingestion of sulfoxone or 8-amino-quinolines, partial GR deficiency has been reported.[15,16] The frequency of partial deficiency has also been reported in some populations including Sudanese,[17] Spanish,[18] European-American, Afro-American, Iranian, and South Vietnamese.[19]

In the Saudi population, we encountered partial GR deficiency in a study conducted in the Eastern and Southwestern Provinces, and due to the high prevalence of sickle cell and G6PD deficiency genes, several cases with two or more associated red cell genetic defects were encountered.[6]

This study in Riyadh, an area which has been regarded as a malaria-free zone by the Ministry of Health,[20] shows a considerably lower frequency of G6PD deficiency and Hb S gene,[7,8] and the overall partial GR deficiency in Riyadh is significantly lower than in Hofuf. However, when compared with results obtained in Khaibar, the frequency of GR deficiency in females in both areas is similar, although the frequency in males in Riyadh is slightly lower than that in Khaibar (Table 3). Since the frequency of Hb S and G6PD deficiency gene are very low in this area, interaction between GR deficiency and these red cell genetic abnormalities is not encountered, though cases with associated GR deficiency and α-thalassemia are seen and the hematologic values and the red cell indices are influenced by the presence of α-thalassemia.

Comparison of the hematologic values in nonthalassemic GR-deficient and normal individuals showed that the total red blood cell count and packed cell volume was lower in GR-deficient individuals (both male and female) compared to normal individuals. Total hemoglobin, on the other hand, was slightly higher in GR-deficient males, but lower in GR-deficient females com-

TABLE 3. *Mean hematologic values in GR-deficient α-thalassemic and nonthalassemic individuals.*

		Hematologic values (mean ± SD)					
	No. investigated	RBC ($\times 10^{12}$/L)	Hb (mmol/L)	PCV (L/L)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
Male							
Thalassemic	3	5.15 ± 0.48	± 7.59 ± 1.70	0.33 ± 0.06	68.0 ± 8.5	1.40 ± 0.31	22.54 ± 2.58
Nonthalassemic	17	5.01 ± 0.54	9.74 ± 0.49	0.38 ± 0.03	84.0 ± 2.5	1.93 ± 0.21	25.50 ± 1.88
Female							
Thalassemic	3	4.54 ± 0.40	6.86 ± 0.25	0.33 ± 0.012	74.3 ± 5.0	1.51 ± 0.12	20.47 ± 0.62
Nonthalassemic	8	4.40 ± 0.53	7.88 ± 0.61	0.38 ± 0.04	87.6 ± 4.0	1.81 ± 0.09	20.85 ± 0.62

pared to normals. The red cell indices, i.e., MCV, MCH, and MCHC, were similar in both GR-deficient and normal individuals. The only exception was MCHC, which was significantly higher in males. The reason for the elevation of MCHC is not clear. It appears that since there was a reduction in the total red blood cell count, the total hemoglobin level was elevated, though in females a similar elevation did not occur. Between the α-thalassemic and nonthalassemic groups, the major difference was encountered in the level of the red cell indices, hemoglobin, and packed cell volume levels, which were reduced significantly in the thalassemic group.

In conclusion, this study has shown that partial GR deficiency exists in the population of Riyadh and complete GR deficiency is rare. Interaction between GR deficiency and α-thalassemia is encountered, but no cases of associated GR deficiency and sickle cell gene or G6PD deficiency were seen, in contrast to the results from the Eastern and Southwestern Provinces. This can be explained on the basis of low frequency for these genes in the Riyadh population compared to the two other areas investigated earlier.

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References

1. Waller HD. Glutathione reductase deficiency. In: Beutler E, ed. Hereditary disorders of erythrocyte metabolism. New York: Grune & Stratton, 1968:185.
2. Staal GE, Helleman PW, van Milligen-Boersma L, et al. Properties of glutathione reductase purified from erythrocytes with normal and with diminished activity of the enzyme. Nederl T Geneesk 1968;112:1008-9.
3. Jaffe ER, Rieber EE, Anderson HM, et al. Glutathione reductase activity and hemolysis in hemoglobin C diseases. J Clin Invest 1968;47:51a.
4. Flatz G. Population study of erythrocyte glutathione reductase activity: I. Stimulation of the enzyme by flavin adenine dinucleotide and by riboflavin supplementation. Hum Genet 1971;11:269-77.
5. Goebel KM, Goebel FD. Hemolytic anemia and pancytopenia in glutathione reductase deficiency: further experience with riboflavin. Acta Haematol 1972;47:292-6.
6. El-Hazmi MA, Warsy AS. Glutathione reductase deficiency in association with sickle cell and thalassaemia genes in Saudi populations. Hum Hered 1985;35(5):326-32.
7. El-Hazmi MAF. Haemoglobin disorders: a pattern for thalassaemia and haemoglobinopathies in Arabia. Acta Haematol 1982;68(1):43-51.
8. El-Hazmi MAF. The distribution and nature of hemoglobinopathies in Arabia. In: Bowman JE, ed. Distribution and evolution of hemoglobin and globin loci. New York: Elsevier, 1983:66-77.
9. Dacie JV, Lewis SM. Practical haematology, 5th ed. London: Churchill Livingstone, 1975:42.
10. Marengo-Rowe AJ. Rapid electrophoresis and quantitation of haemoglobins on cellulose acetate. J Clin Pathol 1965;18:790-2.
11. Betke K, Marti HR, Schlicht L. Estimation of small percentage of foetal haemoglobin. Nature 1959;184:1877-8.
12. Beutler E. Red cell metabolism: a manual of biochemical methods, 2nd ed. New York: Grune & Stratton, 1975:69-70.
13. Tillotson JA, Baker EM. An enzymatic measurement of the riboflavin status in man. Am J Clin Nutr 1972;25:425-31.
14. Beutler E. Glutathione reductase. In: Hemolytic anemia in disorders of red cell metabolism. New York: Plenum Press, 1978.
15. Desfroges JF, Thayer WW, Dawson JP. Hemolytic anemia induced by sulfoxone therapy, with investigations into the mechanism of its production. Am J Med 1959;127:132-6.
16. Carson PE, Brewer GJ, Ickes C. Decreased glutathione reductase with susceptibility to hemolysis (abstract). J Lab Clin Med 1961;58:804.
17. Saha N. Erythrocyte glutathione reductase polymorphism in a Sudanese population. Hum Hered 1981;31(1):32-4.
18. Garcia SC, Moragon AC, Lopez-Fernandez ME. Frequency of glutathione reductase, pyruvate kinase and glucose-6-phosphate dehydrogenase deficiency in a Spanish population. Hum Hered 1979;29(5):310-3.
19. Frischer H, Bowman JE, Carson PE, et al. Erythrocytic glutathione reductase, glucose-6-phosphate dehydrogenase and 6-phosphogluconic dehydrogenase deficiencies in populations of the United States, South Vietnam, Iran and Ethiopia. J Lab Clin Med 1973;81:603-12.
20. Malaria Control Programme in the Kingdom. General Directorate of Preventive Medicine, Ministry of Health, Kingdom of Saudi Arabia. Riyadh: Bahr Al-Olum Press, 1983:27.

THE ROLE OF CHEST ROENTGENOGRAPHY IN THE MANAGEMENT OF FEBRILE CHILDREN WITH RESPIRATORY SIGNS AND SYMPTOMS

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روجعت صور الصدر بأشعة رونتجن لـ ٢٢٨ طفلا يعانون من الحمى مع أعراض وعلامات تنفسية متنوعة. كان السعال فقط، الى جانب الحمى، موجودا لدى نسبة ٤٠ر٤٪ من المرضى. وكانت نسبة ٨ر٣٪ فقط تعاني من الحمى ومزيج من الأعراض والعلامات (سعال، فرقعات وصعوبة التنفس). وقد لوحظت علامات شاذة في صور الصدر بأشعة رونتجن لـ ١٢٢ مريضا. ووجدت المظاهر الإشعاعية الأكثر تواردا لدى ١٠٥ مرضى وكان وضعها في الرئة اليمنى أكثر منه في اليسرى. وكانت الفصوص السفلى اكثر تأثرا من الفصوص الأخرى. وقد تم حساب الخطورة النسبية لحدوث المظاهر المرضية على صورة الصدر من العلامات والأعراض المختلفة وتبين أن الذين يعانون من أعراض وعلامات سريرية مختلطة هم أكثر تعرضا لظهور علامات مرضية على صورة الصدر. كان تسرع التنفس هو العلامة المنعزلة الوحيدة المصحوبة بمظاهر مرضية على صورة الصدر.

Chest roentgenograms of 228 febrile children with various respiratory signs and symptoms were reviewed. Cough alone, in addition to fever, was present in 40.4% of the patients. Only 8.3% had fever and a combination of signs and symptoms (cough, crepitations, and difficulty in breathing). One hundred twenty-two patients had abnormal findings on chest roentgenograms. The commonest abnormal radiologic finding was present in 105 patients who had more lesions occurring in the right lung than the left. The lower lobes were affected more than other lobes. The relative risk of having abnormal findings on chest roentgenograms was calculated for the various symptoms and signs. Patients with a combination of signs and symptoms were more likely to have abnormal roentgenographic findings. Tachypnea was the only single sign that was associated with an abnormal radiographic appearance.

The febrile child is frequently a problem in the pediatric emergency room. As part of the initial investigation of some of these patients, a chest roentgenogram is often requested, ostensibly to exclude pneumonia as the cause of the illness. However, the World Health Organization has stated that in the management of sick children without clinical evidence of cardiopulmonary disease, a chest roentgenogram is not helpful.[1] Furthermore, WHO states that a lateral projection of the chest roentgenogram should be used only for additional information that would influence the management of the patient.[1]

This study was undertaken to assess the relevance of the above statements as they relate to the use of chest roentgenography among residents in our hospital in evaluating children with acute febrile illnesses in an attempt to establish a working protocol for such patients.

Patients and Methods

Febrile children with temperature of at least 39°C in addition to symptoms and signs suggestive of a respiratory tract illness were enrolled in the study. Febrile children without signs and symptoms of respiratory illness were excluded

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because they are not routinely submitted to chest roentgenography in our unit. Children known to have chronic respiratory illness and any history or signs of inhaled foreign body were also excluded from the study.

All the patients were seen by pediatric residents in the emergency room of King Khalid University Hospital, Riyadh, between October 1984 and September 1985. The patients included in the study were identified by retrospective review of the emergency room log book. The relevant data recorded prior to radiography were abstracted from the chart as well as the original x-ray form of each patient. The chest roentgenograms were evaluated jointly by radiologists. The radiographic findings on each film were recorded as normal or abnormal. Abnormal findings were categorized further with regard to type of lesion and its location.

Roentgenographic findings and the presenting symptoms and signs were matched. The relative risk (or odds ratio) for each symptom or sign and for the combination of symptoms and signs was estimated using the method of Lilienfeld[2] to assess their association with the roentgenographic findings.

Results

During the study period, 228 febrile children had chest roentgenograms done as part of their initial investigation. There were 135 males and 93 females (M:F = 1.45:1). Their ages ranged from 10 days to 12 years with 134 (59%) of them being below 2 years of age (Figure 1).

The signs and symptoms in addition to fever with which the patient presented are summarized in Table 1. Abnormal radiographic findings are shown in Table 2.

The distribution of lesions within the lobes is shown in Figure 2 with lobar or segmental consolidations occurring in 105 (86.1%) out of 122 chest roentgenograms with abnormal findings.

Incidental radiographic findings were an enlarged thymus in eight patients, rickets in three, and bifid rib in one patient.

Table 1 also shows the comparative analysis of signs and symptoms in children with normal and abnormal radiographic findings. We observed that when fever was associated with cough, only

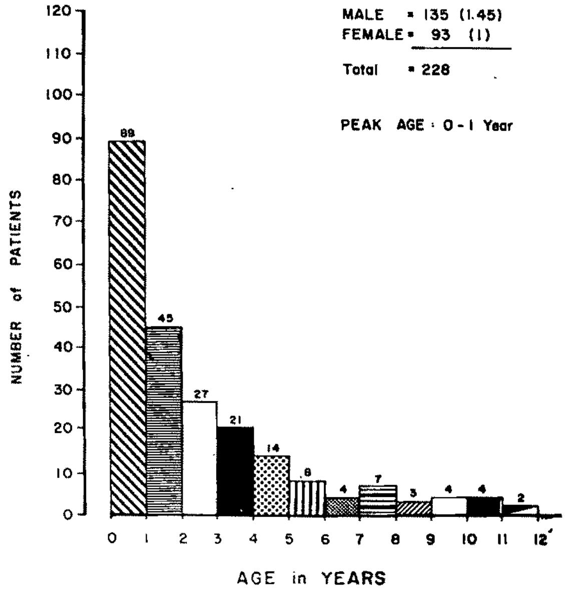

FIGURE 1. Age distribution of the patients.

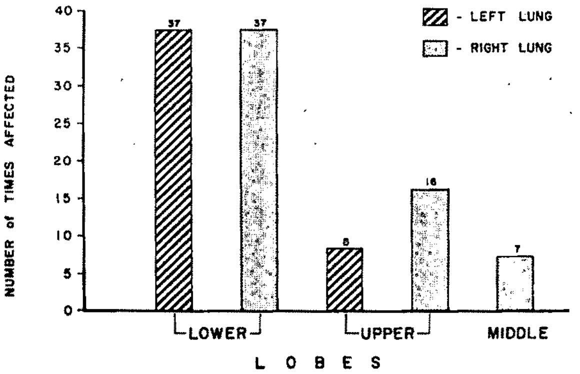

FIGURE 2. Distribution of consolidation in the lung fields.

TABLE 1. *Analysis of symptoms and signs in addition to fever with comparison of normal and abnormal x-ray findings.*

Signs and symptoms	No. of patients (%)	No. of patients in subgroup (%)
Cough	92(40.4)	
Normal x-ray findings		62(67.4)
Abnormal x-ray findings		30(32.6)
Crepitations	66(28.9)	
Normal x-ray findings		34(51.5)
Abnormal x-ray findings		32(48.5)
Difficulty in breathing	51(22.4)	
Normal x-ray findings		8(15.7)
Abnormal x-ray findings		43(84.3)
Combined	19(8.3)	
Normal x-ray findings		2(10.5)
Abnormal x-ray findings		17(89.5)
Total	228(100.0)	228

TABLE 2. *Analysis of 122 patients with abnormal radiographic findings.*

Lesions		No. of patients
Consolidation		105
Single lobe	60	
Multiple lobes	45	
Collapse		6
Right upper lobe	2	
Right lower lobe	3	
Left lower lobe	1	
Adenopathy		6
Right hilar	2	
Bilateral hilar	3	
Anterior mediastinum	1	
Pulmonary edema		1
Interlobar fissure fluid		2
Cardiomegaly		2
Total		122

TABLE 3. *Comparative relative risk values of each sign or symptom complex.*

	Abnormal x-ray findings	Normal x-ray findings	Total
Cough	30	62	92
No cough	92	44	136
Total	122	106	228
Relative risk = 0.2			
Crepitations	32	34	66
No crepitations	90	72	162
Total	122	106	228
Relative risk = 0.75			
Difficulty in breathing	43	8	51
No difficulty in breathing	79	98	177
Total	122	106	228
Relative risk = 6.6			
Combined signs and symptoms*	17	2	19
Incomplete combination of symptoms and signs	105	104	209
Total	122	106	228
Relative risk = 8.4			

*Cough, difficulty in breathing, and crepitations.

32.6% of the patients had chest roentgenograms with abnormal findings. However, when fever was associated with difficulty in breathing, 84.3% had abnormal findings; when cough, difficulty breathing, and crepitations were present together, 89.5% of the patients had abnormal roentgenographic findings.

Table 3 shows the relative risk value of each sign or symptom complex associated with abnormal radiographic findings.

Discussion

The chest roentgenogram has become an almost indispensable part of the investigation of patients. It is requested not only in the presence of signs and symptoms referable to the chest but also in a host of other situations such as acute febrile illnesses and pyrexia of unknown origin, and in our environment, even in patients undergoing elective surgery as well as healthy people having annual check-ups.[3] Modern concepts of practice do not favor the indiscriminate use of chest roentgenography in some of these circumstances.[1,4] In the investigation of pyrexia of unknown origin, it could be argued that a normal-appearing chest radiograph is an important "negative" finding, particularly in societies where medicolegal implications have a significant influence on established clinical practice. In dealing with the acutely febrile child, however, discriminate use of the chest radiograph is more desirable and efficacious.

There have been few studies on the radiographic findings in febrile children.[3,5-7] Most of these have been done in North America and Europe, with none in the Arab world, where the geographic distribution and incidence of disease are different. The efficacy of chest radiographs in children and the disease pattern demonstrated thus become relevant to the management of such cases in this region.

The age distribution of the patients in this study shows that 59% of them were below the age of 2 years. This proportion is similar to that reported by Leventhal.[3] This is expected since a febrile illness in a young child who was previously well is likely to arouse parents and cause them to seek prompt medical advice.

The commonest presenting symptom was cough (40.4%). Difficulty in breathing was seen in 22.4% of cases. Fever and crepitations, without cough, were found in 28.9% of the patients. Only 8.3% presented with fever in combination with cough, difficulty in breathing, and crepitations (Table 3).

In a recent study, out of 19 febrile patients with respiratory distress, seven patients had abnormal findings on chest radiography. That is, the positive predictive value of respiratory signs was 37%.[7] In our study, the positive predictive value was 53.5% (122 radiographs with abnormal findings out of 228 patients with respiratory distress). The explanation for this difference may be that in the study of Heulitt et al, the sample was small and the age of the children not comparable, being under 3 months.[7]

Lobar consolidation was present in 88% of cases. The right lung was affected more often that the left. However, the lower lobes were affected equally. These findings correlate well with those of Highman,[6] due to the anatomical arrangement of the right upper lobe bronchus which allows poor drainage in the supine position. We also suggest that, in our environment, this anatomic factor may be aided by the usual practice of positioning infants on the left arm of the predominantly right-handed mothers, while they are being carried or cuddled. This position favors aspiration of feeds into the right lung, particularly in bottle-fed infants.

The relative risk values were highest in patients with the combined signs and symptoms, being 8.4 and to a lesser extent in those with difficulty in breathing with a value of 6.6. The values in those with cough or crepitations alone were quite low (Table 3). These observations are similar to those of Leventhal.[3] In that study, tachypnea or a cluster of pulmonary findings was the best predictor of pneumonia, as defined by appropriate abnormal chest roentgenographic findings.

It should be noted that in very young children, difficulty in breathing, which is usually manifested as tachypnea, is an important pulmonary sign, the presence of which increases the likelihood of an abnormal chest radiograph.

Cough and crepitations by themselves, according to this study, are not good determinants in predicting which roentgenograms will have abnormal findings. This is explained by the fact that cough may be a sign of upper respiratory infection without involvement of the lung parenchyma. Crepitations may also reflect bronchiolar inflammation or transient and small amounts of alveolar fluid collection which may not be associated with abnormal radiographic findings.

The abnormal lung findings seen in some of the roentgenograms were not suspected on the basis of the clinical findings. Six patients had segmental or lobar collapse in the lungs. The reasons for the collapse were not obvious, but secretions may have blocked some brochioles. The patient who had pulmonary edema had a history of kerosene ingestion in addition to fever and tachypnea. This is not an unexpected finding.[8] The two patients with fluid in the interlobar fissure had only fever and cough, and the finding was unexpected.

Two sickle cell disease patients with fever and cough had radiologic evidence of cardiomegaly. They had no other symptoms suggestive of cardiac disease. However, their basic illness (sickle cell anemia) could account for the cardiomegaly. The six children with hilar adenopathy had tuberculosis. Failure to identify these patients with tuberculosis would have been serious. Perhaps a more detailed history could have identified them as appropriate candidates for chest radiography.

Since most of our patients were young infants, it was not surprising that eight of them had large thymus gland. Bifid rib is a minor congenital abnormality, and its presence had no obvious relationship with the presenting complaints nor was it associated with other abnormalities. Rickets is common in young children in our environment,[9] and it is not surprising that three undiagnosed cases were encountered; two of these children had normal roentgenographic findings while the third had right upper lobe consolidation. In all three children, crepitations were heard in both lung fields which prompted the chest radiography. The unexpected presence of rickets in these three children is an important finding.

In none of the 43 patients in whom lateral views were done did the lateral view add any information which was not apparent on the posteroanterior view. This finding lends support to the WHO recommendation[1] that the lateral projection should not be used routinely unless it is judged that it would yield additional information which may significantly influence the management of the patient. Lateral or additional views should only be requested by the radiologist when available. It has also been observed that the more experienced a pediatrician is in interpreting the posteroanterior view correctly, the more likely he or she is to avoid requesting the lateral projection. However, since most busy pediatric emergency rooms are staffed by junior physicians[10] and since only few emergency rooms are covered on a 24-hour basis by a radiologist-in-residence, lectures in radiology for undergraduate medical students and continuing education in diagnostic radiology for physicians should be routine practice. This will improve the quality of requests and the understanding of the information that can be gained from a given radiologic examination.

In conclusion, our study shows that in evaluating acutely febrile children in the emergency room, careful history and physical examination usually provide the basis to predict the likelihood of abnormal findings on chest roentgenograms. (Early diagnosis ensures early treatment.) Thus, the quality of management is enhanced by submitting those children with relevant signs to roentgenographic examination. The lateral chest roentgenogram, even though an inexpensive procedure with low radiation dose to sensitive areas, rarely adds information to what is provided by the posteroanterior view. Such additional information, even when available, seldom affects treatment decisions in the emergency room.

Attention to these facts will help in limiting the radiation exposure of children and in improving the cost-effectiveness as well as efficacy of chest roentgenograms in general.

References

1. World Health Organization Scientific Group. A rational approach to radiodiagnostic investigations: a report of a WHO scientific group on the indications for and limitations of major x-ray diagnostic investigations. WHO Tech Rep Ser 1983;689:17-9.
2. Lilienfeld AR. Foundations of epidemiology. New York: Oxford University Press, 1976.
3. Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. Clin Pediatr 1984;21(12):730-4.
4. Brill PW, Ewing ML, Dunn AA. The value (?) of routine chest radiography in children and adolescents. Pediatrics 1973;52:125-7.
5. McCarthy PL, Spiesel SZ, Stashwick CA, et al. Radiographic findings and etiologic diagnosis in ambulatory childhood pneumonias. Clin Pediatr 1981;20(11):686-91.
6. Highman JH. Chest infection in childhood. Clin Radiol 1970;21:52-61.
7. Heulitt MJ, Ablow RC, Santos CC, et al. Febrile infants less than 3 months old: value of chest radiography. Pediatric Radiology 1988;167:135-7.
8. Eade NR, Taussig LM, Marks MI. Hydrocarbon pneumonitis. Pediatrics 1974;54(3):351-7.
9. El-Idrissy ATH, Taha SA. Rickets in Riyadh. Proceedings of the 5th Saudi medical meeting, Riyadh, 1980:409-18.
10. Baker MD. Physician coverage in the pediatric emergency room: a national survey. Am J Dis Child 1986;140:755-7.

IN VITRO SUSCEPTIBILITY OF RELATIVELY RESISTANT BACTERIA TO IMIPENEM

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تم اختبار فعالية «امبينيم» في الأنبوب ضد ٩٦٥ عينة سريرية من الجراثيم المعزولة من مركز إحالة رئيسي في المملكة العربية السعودية. وكان عدد من هذه الذراري شديد المقاومة للمضادات الحيوية الشائعة كالأمبيسيلين وسيفالوسبورين وجنتامايسين وبايبرسيلين وتيكارسيلين. وقد كانت جميع الجراثيم المعزولة (٧٢٧) من الامعائيات والاسينتوباكتر والعنقودية الذهبية والمكورات المعوية وغيرها من العقديات متأثرة بالأمبينيم. كما كانت غالبية ذراري الزائفة الزنجارية (٩٥٪) والعنقودية البشروية (٩٠٪) مثبطة بالكاربينم. أبدت ٩ معزولات من بين ١١ معزولة من الزوائف غير الزنجارية مقاومة لهذا المضاد الحيوي.

In vitro activity of imipenem was tested against 965 clinical isolates from a major referral center in Saudi Arabia. Many of these strains were highly resistant to commonly used antibiotics, such as ampicillin, cephalosporins, gentamicin, piperacillin, and ticarcillin. All the 727 isolates of Enterobacteriaceae, *Acinetobacter*, *Staphylococcus aureus*, enterococci, and other streptococci were susceptible to imipenem. The majority of the strains of *Pseudomonas aeruginosa* (95%) and *S. epidermidis* (90%) were also inhibited. Nine of the 11 isolates of pseudomonads other than *P. aeruginosa* were resistant to this antibiotic.

Imipenem (N-formimidoylthienamycin monohydrate) is a new thienamycin antibiotic produced by *Streptomyces cattleya*. Although it contains a beta-lactam ring, structurally, it is quite distinct from the penicillins, cephalosporins, and cephamycins. This unique structural difference of imipenem is apparently responsible for its having the broadest antimicrobial activity of currently available beta-lactam antibiotics and for its resistance to hydrolysis by chromosomal or plasmid-mediated beta-lactamases.[1-4]

Imipenem has been studied extensively to determine its efficacy in treating a wide variety of infections.[5-12] In vitro studies have shown that imipenem has excellent activity against both gram-positive and gram-negative bacteria, aerobes as well as anaerobes.[1,6,8,13-17] Almost all previous studies were confined to bacterial strains isolated in North America or Europe, where microorganisms are known to be more susceptible to commonly used antibiotics than the strains isolated in Asia, Africa, and South America.[18-24]

In this paper, we report the susceptibility pattern of clinical isolates from a major referral center in Saudi Arabia to imipenem and compare this pattern with those of other commonly used antibiotics.

Materials and Methods

Microorganisms

A total of 965 consecutive isolates from clinical specimens at King Faisal Specialist Hospital and Research Centre, Riyadh, were used in this investigation. The isolates consisted of 663 gram-negative rods and 302 gram-positive bacteria. These isolates were obtained from blood cultures,

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urines, respiratory tracts, wounds, tissues, body fluids, and other miscellaneous sources.

Antimicrobial Agents

Commercially prepared antibiotic disks were used during this investigation. Potency of antibiotics used were as follows: 30 μg for amikacin, ceftazidime, ceftriaxone, cephalothin, cefoxitin, chloramphenicol, nitrofurantoin, and vancomycin; 10 μg for colistin, ampicillin, and gentamicin; 100 μg for piperacillin; 2 μg for clindamycin; 1.25/23.75 μg for trimethoprim/sulfamethoxazole; 10 units for penicillin G; and 1 μg for oxacillin. The disk content and interpretative data for imipenem (10 μg) were provided by the manufacturer (Merck, Sharp and Dohme); for other antimicrobial agents, the criteria established by the National Committee for Clinical Laboratory Standards (1984) were used.

All the bacteria were tested by the standard conventional disk diffusion test. Mueller-Hinton agar with a pH between 7.2 and 7.4 was used to perform disk diffusion susceptibility testing. Inoculated plates were incubated at 35°C for 18 to 24 hours. *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control organisms.

Results

The susceptibility pattern of 663 gram-negative clinical isolates to imipenem and 13 other commonly used antimicrobial agents is shown in Table 1. All the members of the Enterobacteriaceae family, including *Serratia marcescens*, *Acinetobacter*, and *Aeromonas* organisms, were inhibited by imipenem. No other antibiotic was found to be as active.

Of the 137 strains of *P. aeruginosa* tested, almost 95% were sensitive to imipenem. Five of the seven other species of *Pseudomonas* were also inhibited by this thienamycin. However, the antibiotic did not inhibit any of the four strains of *P. maltophilia* isolated in our laboratories.

All of the 128 strains of *S. aureus* were inhibited by imipenem as were enterococci and other streptococci (Table 2). Seventy-eight of the 87 *S. epidermidis* isolates were also found to be susceptible to imipenem. The only antibiotic that was found to be as effective or superior for *S. epidermidis* was vancomycin.

Discussion

Both gram-negative and gram-positive bacteria isolated from clinical specimens appear to be more resistant to commonly used antimicrobial agents in developing countries.[19,20,24,25] Qadri et al[22,23] reported that gram-negative bacteria, especially *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus*, and *Serratia*, were significantly more resistant to commonly used antimicrobial agents in Saudi Arabia than in the United States. This study was therefore carried out to determine the in vitro effectiveness of imipenem against such resistant bacteria.

Earlier studies have shown excellent in vitro activity as well as successful imipenem treatment of complicated and uncomplicated infections. Although the bacteria tested in this investigation were more resistant to ampicillin, carbenicillin, cephalosporin, gentamicin, piperacillin, and trimethoprim/sulfamethoxazole, 99% of the gram-negative organisms were inhibited by imipenem. In our experience, the only bacteria that showed resistance to imipenem were pseudomonads other than *P. aeruginosa*, which is consistent with previous reports.[6,14]

Initial therapeutic regimens in many infections of suspected bacterial etiology include aminoglycosides because many of the penicillins or cephalosporins are inactivated by beta-lactamases, or some of them have virtually no activity against important pathogens like *P. aeruginosa*, *Enterobacter*, *Serratia*, and *S. aureus*.[4,7,14,26,27] Although aminoglycosides are highly effective, their major drawbacks are possible ototoxicity or nephrotoxicity.[28] During this study imipenem was found to be comparable or superior to gentamicin and amikacin, inhibiting the growth of all members of the Enterobacteriaceae family, *Acinetobacter* organisms, *S. aureus*, enterococci, and 95% of *P. aeruginosa* strains. In essence, imipenem provides a safer drug like penicillin, with the efficacy of toxic aminoglycosides but without the drawback of many other beta-lactams which are inactivated by bacterial penicillinases.

TABLE 1. *Antibacterial activity of imipenem and other antibiotics against gram-negative bacteria.*

	% Susceptible*													
Organisms (No. tested)	IPM	AN	AM	TIC	CR	CFOX	C	FUR	GM	PIP	SXT	COLIS	CAZ	CRO
Escherichia coli (225)	100	95.5	36.9	39.6	79.4	97.8	62.9	94.9	94.2	46.6	57.1	100	100	100
Klebsiella pneumoniae (87)	100	97.7	4.6	5.81	85.1	96.6	78.2	34.4	81.6	75.9	89.7	100	100	100
K. oxytoca (11)	100	100	9.1	36.4	45.5	100	72.7	–	81.8	81.8	72.7	100	100	100
Pseudomonas aeruginosa (137)	94.9	91.2	–	77.4	–	–	–	–	71.5	82.5	–	98.3	91.7	47.7
P. maltophilia (4)	0	75.0	–	25.0	–	–	–	–	50.0	25.0	–	100	25.0	0
Pseudomonas sp. (7)	66.7	57.1	–	28.6	–	–	–	–	14.3	71.4	–	57.1	66.7	40.0
Proteus mirabilis (37)	100	100	35.1	91.9	35.1	91.9	41.7	–	94.6	100	75.7	–	100	100
P. penneris (3)	100	100	0	33.3	0	66.7	33.3	–	100	100	66.7	–	–	–
P. vulgaris (6)	100	100	16.7	83.3	16.7	100	83.3	–	100	83.3	66.7	50.0	100	100
Enterobacter agglumerans (3)	100	100	0	33.3	66.7	100	100	–	100	100	100	–	–	–
E. cloacae (39)	100	89.7	5.1	56.4	7.7	15.4	56.4	73.3	79.5	66.7	74.4	81.8	81.8	100
E. aerogenes (8)	100	100	12.5	75.0	25.0	28.6	75.0	50.0	100	75.0	83.3	–	–	–
Enterobacter sp. (3)	100	100	0	33.3	0	0	33.3	100	33.3	33.3	0	66.7	50.0	–
Citrobacter freundii (11)	100	100	18.1	63.6	18.9	27.3	63.6	62.5	81.8	63.6	72.7	–	100	100
Citrobacter sp. (4)	100	100	0	25.0	50.0	100	100	–	100	100	100	–	–	–
Acinetobacter calcoaceticus var. *anitratus* (7)	100	57.1	0	85.7	0	14.3	0	–	28.6	85.7	50.0	100	75.0	66.7
A. calcoaceticus var. *lwoffi* (6)	100	100	16.7	100	0	16.7	16.7	–	100	100	83.3	–	–	–
Providencia sp. (6)	100	100	83.3	100	83.3	100	0	–	66.7	100	100	–	–	–
Serratia marcescens (24)	100	87.5	0	70.8	0	25.0	87.5	0	75.0	83.3	82.6	0	100	100
Serratia sp. (3)	100	100	33.3	0	33.3	100	66.7	–	33.3	33.3	100	50.0	100	100
Shigella sp. (3)	100	100	50.0	50.0	100	100	50.0	–	100	100	50.0	–	–	–
Salmonella sp. (21)	100	100	85.7	85.7	85.7	95.2	95.2	66.7	100	85.7	95.2	–	–	–
Aeromonas hydrophila (2)	100	100	0	0	50.0	100	100	–	100	100	100	–	–	–
Morganella morganii (6)	100	100	16.7	83.3	0	16.7	66.7	0	100	100	50.0	–	100	100

*IPM = imipenem; AN = amikacin; AM= ampicillin; TIC = ticarcillin; CR = cephalothin; CFOX = cefoxitin; C = chloramphenicol; FUR = nitrofurantoin; GM = gentamicin; PIP = piperacillin; SXT = trimethoprim/sulfamethoxazole; COLIS = colistin; CAZ = ceftazidime; CRO = ceftriaxone.

TABLE 2. *Antibacterial activity of imipenem against gram-positive bacteria.*

	% Susceptible*										
Organisms (No. tested)	IPM	AM	CR	C	CC	FUR	GM	OX	PEN	SXT	VA
Staphylococcus aureus (128)	100	4.3	93.2	97.5	92.9	97.5	92.2	91.5	4.3	91.4	100
S. epidemidis (87)	89.6	11.9	92.5	63.1	75.4	97.0	39.7	25.4	11.9	49.3	100
Enterococci (68)	100	97.1	17.7	70.6	8.8	92.7	13.4	–	92.5	80.9	100
Streptococcus pneumoniae (3)	100	100	100	100	100	100	33.3	100	100	100	100
Viridans streptococci (10)	100	50.0	90.0	80.0	100	100	80.0	–	60.0	57.1	100
Nonhemolytic streptococci (3)	100	33.3	33.3	100	33.3	100	100	0	33.3	0	100
Bacillus sp. (3)	100	100	100	100	100	0	100	0	100	100	100

*IPM = imipenem; AM = ampicillin; CR = cephalothin; C = chloramphenicol; CC = clindamycin; FUR = nitrofurantoin; GM = gentamicin; OX = oxacillin; PEN = penicillin; SXT = trimethoprim/sulfamethoxazole; VA = vancomycin.

References

1. Birnbaum J, Kahan FM, Kropp H, Mac Donald JS. Carbapenems, a new class of beta-lactam antibiotics: discovery and development of imipenem/cilastin. Am J Med 1985;78(6A):3-21.
2. Iannini PB, Kunkel MJ, Hilton E, Iannini GM. Imipenem/cilastatin: general experience in a community hospital. Am J Med 1985;78(68A):122-6.
3. Kahan FM, Kropp H, Sundelof JG, Birnbaum J. Thienamycin: development of imipenem/cilastatin. J Antimicrob Chemother 1983;12(suppl D):1-35.
4. Leanza WJ, Wildonger KG, Miller TW, Cristensen BG. N-Acetimidoyl- and N-formimidoylthienamycin derivates: antipseudomonal beta-lactam antibiotics. J Med Chem 1979;22(12):1435-6.
5. Goldstein EJC, Citron DM. Comparative in vitro activity of imipenem and 15 other antimicrobial agents against clinically important aerobic and anaerobic bacteria. Clin Therapeutics 1988;10(5):487-515.
6. Belobraydic KA, Qadri SM. Antimicrobial activity of imipenem against 1386 clinical isolates. Methods Find Exp Clin Pharmacol 1987;8(11):675-8.
7. Broze B, Mees JD, Droissart R, et al. Randomized comparison of imipenem/cilastatin and ceftadizime in the empiric therapy of severe abdominal infections: a multicenter study. Acta Clin Belg 1987;42:431-6.
8. Cox CE, Corrado ML. Safety and efficacy of imipenem/cilastatin in treatment of complicated urinary tract infections. Am J Med 1985;78(6A):92-4.
9. Dickinson G, Rodriguez K, Arcey S, et al. Efficacy of imipenem/cilastatin in endocarditis. Am J Med 1985;78(6A):117-21.
10. Eron LJ. Imipenem/cilastatin therapy of bacteremia. Am J Med 1985;78(6A):95-9.
11. Fass RJ, Freimer EH, McCloskey RV. Treatment of skin and soft tissue infections imipenem/cilastatin. Am J Med 1985;78(6A):110-2.
12. Norwegian Study Group. Imipenem/cilastatin as a new therapy in severe infections, comparison with ceftoxime in combination with metronidazole and cloxacillin. Scand J Infect Dis 1987;19(6):667-76.
13. Berman SJ, Sugihara JG, Nakamurah JM, et al. Multiple-dose study of imipenem/cilastatin in patients with end-stage renal disease undergoing long-term hemodialysis. Am J Med 1985;78(6A):113-6.
14. Jones RN. Review of the in vitro spectrum of activity of imipenem. Am J Med 1985;78(6A):22-32.
15. MacGregor RR, Gentry LO. Imipenem/cilastatin in the treatment of osteomyelitis. Am J Med 1985;78(6A):100-3.
16. Salata RA, Gebhart RL, Palmer DL, et al. Pneumonia treated with imipenem/cilastatin. Am J Med 1985;78(6A):104-9.
17. Van der Auwera P, Van Laethem Y, Defresne N, et al. Comparative serum bactericidal activity against test anaerobes in volunteers receiving imipenem, clindamycin, latamoxef and metronidazole. J Antimicrob Chemother 1987;19:205-10.
18. Farrar WE. Antibiotic resistance in developing countries. J Infect Dis 1985;152(6):1103-6.
19. Finland M. Emergence of antibiotic resistance in hospitals, 1935-1975. Rev Infect Dis 1979;1:4-20.
20. Murray BE, Alvardo T, Kim KH, et al. Increasing resistance to trimethoprim-sulfamethoxazole among isolates of Escherichia coli in developing countries. J Infect Dis 1985;152(6):1107-13.
21. Olarte J, Galindo E. Salmonella typhi resistant to chloramphenicol, ampicillin and other antimicrobial agents: strains isolated during an extensive typhoid fever epidemic in Mexico. Antimicrob Agents Chemother 1973;4:597-601.
22. Qadri SM, Ostrawski SH, Johnson S, Flournoy DJ. Differences in antimicrobial susceptibilities of clinical isolates in Saudi Arabia and the United States. J Natl Med Assoc 1987;79(4):433-7.
23. Qadri SMH, Rizvi WH, Rahman SA, et al. Antimicrobial resistance of Escherichia, Klebsiella, and Pseudomonas in a large metropolitan hospital in Saudi Arabia: comparison with those in U.S.A. J Natl Med Assoc (in press).
24. Shahid NS, Rahaman MM, Haider K, et al. Changing pattern of resistant Shigal bacillus (Shigella dysenteriae type 1) and Shigella flexneri in Bangladesh. J Infect Dis 1985;152(6):1114-9.
25. Bennett JV. Antibiotic use in animals and human salmonellosis (editorial). J Infect Dis 1980;142(4):631-2.
26. Perryman F, Flournoy DJ, Qadri SMH. In vitro activity of moxalactam against pathogenic bacteria and its comparison with other antibiotics. Chemotherapy 1983;29(1):37-42.
27. Qadri SM, Belobraydic KA. Cefotetan, an in vitro comparison with other antibiotics. J Okla State Med Assoc 1987;80(4):232-5.
28. Jackson GG, Arcieri G. Ototoxicity of gentamicin in man: a survey and controlled analysis of clinical experience in the United States. J Infect Dis 1971;124(suppl):130-7.

SOCIODEMOGRAPHIC AND GYNECOLOGIC CHARACTERISTICS AS RISK FACTORS FOR HERPES SIMPLEX VIRUS TYPE 2 INFECTION IN SAUDI WOMEN

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أُجري مسح وبائي مصلي على ألف وخمسمائة وتسع وأربعين سيدة سعودية خلال الفترة ما بين شهري أيلول/سبتمبر ١٩٨٣م وآذار/مارس ١٩٨٨م. اختيرت العينة أساسًا لتحديد الخصائص النسائية والسكانية الاجتماعية لدى السعوديات اللواتي يبدين إيجابية تفاعل المصل للنوع الثاني من حمة الحلأ البسيط. وقد اكتشفت أضداد الحمة لدى ٤٫٣٪ من جمهرة العينة. وكانت أكثر النساء إيجابية للمصل من كبيرات السن والأميات واللاتي يعشن تحت ظروف سكنية سيئة. كما كانت نسبة الخطر أعلى لدى النساء من مجموعة الدخل العالي أو اللاتي سافر أزواجهن إلى الخارج. وأما النساء اللاتي تزوجن ما بين سن ١٥ و ٢٠ عامًا فقد كن أقل تعرضًا لإيجابية أضداد الحمة في المصل. من ناحية ثانية، كانت النساء اللاتي تزوجن مرتين أو أكثر أو من كان أزواجهن متزوجين من اثنتين فما فوق أكثر عرضة للخطر وكذلك الأمر بالنسبة للزوجة الثانية. وقد أظهرت البيانات أن النساء اللواتي لم يسبق لهن أن حملن قط. كن أكثر عرضة لإيجابية المصل ممن حملن أو أجهضن. وكانت النساء اللاتي أجبن في الاستبيان بذكر خمسة حمول فما فوق أكثر عرضة للخطر ممن حملن أقل من ذلك.

A seroepidemiologic survey of 1549 Saudi women was conducted between September 1983 to March 1988. The sample was selected primarily to determine gynecologic and sociodemographic characteristics of Saudi women who had herpes simplex virus type 2 (HSV-2) seropositivity. Antibodies to the virus were detected in 4.3% of the sample. More women with HSV-2 seropositivity were older, illiterate, and lived in poor housing conditions. Also at higher risk were women from the upper income group, and those whose husbands traveled abroad. Women who married and had their first coitus between the age of 15 and 20 years had lower risk of having positive HSV-2 antibodies. However, those who were married twice or more and women whose husbands had two or more other wives were at higher risk. Second ranked wives had higher risk of HSV-2 seropositivity. The data further disclosed that women who had never become pregnant had a higher risk of seropositivity than those who had history of pregnancy, miscarriage, and abortion. Respondents with history of five or more pregnancies were at higher risk than those with fewer pregnancies.

Herpes simplex virus type 2 (HSV-2) is a venereally transmitted virus, and women with attributes which increase the risk of developing cervical cancer also appear to have an increased risk of becoming infected with this virus.[1] Using antibodies to HSV-2 as an indication of past HSV-2 infections, a number of studies have examined the occurrence of infections among women with cervical cancer and among control women.[2] In all studies, the occurrence of HSV-2 antibodies

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increased with age among controls, reaching a maximum between 40 and 50 years. The HSV-2 antibodies were found more frequently among women of lower socioeconomic status.[3,4] Women who had first intercourse at an early age more commonly had HSV-2 antibodies than women who had intercourse at a later age.[1-5] Furthermore, women with multiple partners more frequently had HSV-2 antibodies than women with fewer partners.[1-5]

Since information is not available on sociodemographic and coital attributes and serologic evidence of HSV-2 infection among Saudi women, this study presents the characteristics of Saudi women with HSV-2 seropositivity. It examines the effects of socioeconomic status, age at first marriage and first coitus, marital status, pregnancy, use of contraceptives, and rank order as wife with regard to the risk of infection with HSV-2.

Materials and Methods

The study sample comprised 1549 nonpregnant Saudi women who attended the gynecology clinic at King Khalid University Hospital, Riyadh, for various gynecologic complaints from September 1983 to March 1988. The sampled women were not selected on the basis of any particular medical reasons. They were chosen randomly to ensure a nonbiased sample.

A blood sample was obtained from each woman, and a standard questionnaire was administered by a trained female interviewer. Each woman was assigned a code number, and the blood samples and questionnaire included items regarding age, race, education, occupation, income, type of housing, age at first sexual exposure, and age at first marriage. Furthermore, data were obtained on the number of marriages of each sampled woman and her husband, as well as number of pregnancies and reproductive wastage measured by number of miscarriages (spontaneous abortions), abortions (induced), and stillbirths, and use of contraceptives. Information was also collected on some other possibly relevant variables such as the husband's traveling habits, number of husband's present other wives, and wife rank order of the subject. The distribution of each risk factor and other possible relevant attributes was compared between seropositive and seronegative groups. The unadjusted risk ratio of HSV-2 seropositivity was calculated by conventional methods.[6] The quantities calculated were for comparison within each variable.

The blood sample was analyzed by indirect fluorescent antibody (IFA) test for detection and titration of antibodies to HSV-1 and HSV-2.[7-9] Detection of very high antibody titer to either type of herpes was not used as the sole criterion or determinant for the primary infection unless the antibody titer to the heterologous virus type was negative. This is because they share a common antigen which might cause an anamnestic response of preexisting antibody to other types.

Results

The most frequently reported reason for attending the clinic among the sampled Saudi women was "check-up after delivery"; this accounted for about half of the sample (49.5%). Other frequently stated reasons were related to "primary infertility" (6.5%), "secondary infertility" (5.1%), "menstrual irregularity" (4.4%), and "abdominal pain" (4.3%). Concerns related to family planning methods and use of contraceptives (such as birth control pills and intrauterine devices) were cited by 6.2% of the sampled respondents. The rest of the sampled women cited various reasons such as back pain, bleeding, general check-up, and others.

The overall results of the viral serology among the sampled Saudi women showed that 97.6% had HSV-1 antibodies, while 66 women (4.3%) had HSV-2 antibodies.

Sociodemographic Factors

Further comparisons of the HSV-2 seropositive and seronegative groups with various sociodemographic factors of the sampled Saudi women are shown in Table 1. Overall, the majority of respondents (56.4%) included in the sample were 20 to 29 years old. The educational level of the sample was generally above the national average: 32.5% had completed secondary education or college. The sampled women mostly came from middle-class families, with nearly half of them having average monthly family income of SR5000 to 9999. Almost two-thirds of them (62.6%) lived

TABLE 1. *Distribution of sociodemographic variables among seropositive and seronegative Saudi women.*

Sociodemographic variable (% of study sample)	HSV-2 antibody Positive (n=66) No. (%)	HSV-2 antibody Negative (n=1483) No. (%)	Risk ratio
Age (y) at interview			
< 20 (7.4)	4(6.1)	111(7.5)	1.00
20–29 (56.4)	31(47.0)	843(56.8)	1.02
30–39 (27.2)	21(31.8)	400(27.0)	1.46
⩾ 40 (9.0)	10(15.1)	129(8.7)	2.15
Educational level			
Secondary and college (32.5)	23(34.8)	480(32.4)	1.00
Elementary (37.9)	17(25.8)	570(38.4)	0.62
Illiterate (29.6)	26(39.4)	433(29.2)	1.25
Family monthly income			
< SR5000 (25.6)	16(24.2)	380(25.6)	1.00
SR5000–9999 (47.4)	27(40.9)	707(47.7)	0.91
⩾ SR10,000 (25.9)	22(33.3)	379(25.6)	1.38
No answer (1.1)	1(1.5)	17(1.1)	–
Type of housing			
Villa (62.6)	39(59.1)	930(62.7)	1.00
Flat (34.7)	22(33.3)	516(34.8)	1.02
Other (2.4)	4(6.1)	34(2.3)	2.18
No answer (0.3)	1(1.5)	3(0.2)	–

TABLE 2. *Distributlion of husband's occupation and overseas travel among seropositive and seronegative Saudi women.*

Husband's occupation and overseas travel (% of study sample)	HSV-2 antibody Positive (n=66) No. (%)	HSV-2 antibody Negative (n=1483) No. (%)	Risk ratio
Husband's occupation			
Skilled worker and laborer (16.0)	7(10.6)	241(16.2)	1.00
Clerical worker (36.7)	21(31.8)	548(37.0)	1.32
Professional and administrator (44.4)	36(54.5)	652(44.4)	1.90
No answer (2.8)	2(3.0)	42(2.8)	–
Overseas travel			
No (64.0)	38(57.6)	953(64.3)	1.00
Yes (34.7)	26(39.4)	511(34.4)	1.28
No answer (1.3)	2(3.0)	19(1.3)	–
*Countries visited**			
Middle East (20.3)	3(11.5)	106(20.7)	1.00
Asia (25.3)	5(19.2)	131(25.6)	1.35
Europe and North America (70.6)	20(76.9)	359(70.3)	1.97
Africa (25.0)	8(30.8)	126(24.7)	2.24

*Percentages are calculated among those husbands who traveled overseas during past 12 months, and they do not total 100% because some husbands traveled to multiple locations.

in villas, 34.7% lived in apartment flats, and the rest (2.4%) lived in mud houses, huts, or tents.

The data indicated that there were relatively more females with positive HSV-2 antibody among the older age groups than the younger ones. Illiterate respondents and those living in poor housing conditions also showed a higher rate of seropositivity. However, respondents in the upper income group had a higher rate of HSV-2 seropositivity than the other income groups. In comparing sociodemographic variables, subjects over 40 years old and those who lived in substandard housing were at higher risk than the others; both groups had risk ratio exceeding a factor of 2.

Husband's Occupation and Overseas Travel

Most of the respondents' spouses were businessmen, managers, or professionals (44.4%). Women whose husbands were in the upper occupational categories had a relatively higher risk of HSV-2 seropositivity (Table 2).

About 34.7% of the husbands had traveled to foreign countries during the past 12 months. Among this group of travelers, 70.6% had traveled to Europe or North America, about one quarter of husbands had visited different Asian or African countries, and 20.3% went to other Middle Eastern countries. The respondents whose husbands had traveled abroad during the past 12 months were also slightly more at risk; those women whose husbands had traveled to Europe, North America, and Africa appeared to be associated with higher risk ratios of HSV-2 seropositivity.

Marriage and Coitus

The average age at first marriage of the sampled women was 18.26 years old. About 14.4% of the women were married at the age of 14 years or younger, and overall 81.6% first married before they reached 20 years of age. The distribution of reported age at first intercourse of the respondents was almost identical to that of age at first marriage. Comparisons of the viral serology results among the different age groups at first marriage and coitus (Table 3) indicated that the youngest age group (less than 15 years) had slightly higher risk ratios than the older ones. Those who first married and had intercourse between the ages of 15 and 20 had lower risk of having positive HSV-2 antibodies.

Marital Status

About 97.7% of the sampled women were married at the time of interview, while 1.9% were divorced, separated, or widowed. Only 0.4% of the respondents failed to answer this question. Among those who had married, only 11.2% had married more than once, while 6.4% of their husbands currently had other wives, and more than half of this group were the first wife in the rank order.

The analysis presented in Table 4 suggests that the high-risk groups were among the women who married more than twice and those whose husbands had two or more other wives at the same time; their risk ratios were 2.39 and 3.81, respectively. Second-ranking wives had a slightly higher risk of HSV-2 seropositivity.

Child Bearing and Pregnancy Wastage

Overall, 11.3% of the respondents had never become pregnant, while the majority of the women (52.5%) had experiened three or more pregnancies. In addition, 30.4% of the respondents had history of miscarriage, and only 3.2% had ever had an abortion.

When the results of viral investigation of HSV-2 antibodies were compared with the child-bearing pattern (Table 5), the data indicated that the women who had never become pregnant had relatively higher risk of seropositivity than those who had history of pregnancy, miscarriage, and abortion. Among those who had pregnancy records, the respondents with five or more pregnancies were more at risk than those with fewer number of previous pregnancies.

TABLE 3. *Distribution of age at first marriage and coitus among seropositive and seronegative Saudi women.*

Age (y) at first marriage and coitus (% of study sample)	HSV-2 antibody: Positive (n=66) No. (%)	Negative (n=1483) No. (%)	Risk ratio
First marriage			
> 20 (17.8)	13(19.7)	263(17.7)	1.00
18 – 20 (30.3)	15(22.7)	455(30.7)	0.67
15 – 17 (36.9)	23(34.8)	549(37.0)	0.85
< 15 (14.4)	15(22.7)	208(14.0)	1.46
No answer (0.5)	0	8(0.5)	–
First sexual exposure			
> 20 (17.9)	14(21.2)	264(17.8)	1.00
18 – 20 (30.2)	15(22.7)	453(30.5)	0.62
15 – 17 (37.0)	23(34.8)	550(37.1)	0.79
< 15 (14.2)	14(21.2)	206(13.9)	1.28
No answer (0.6)	0	10(0.7)	–

TABLE 4. *Distribution of marital status among seropositive and seronegative Saudi women.*

Marital status (% of study sample)	HSV-2 antibody: Positive (n=66) No. (%)	Negative (n=1483) No. (%)	Risk ratio
No. of previous marriages			
None (88.8)	57(86.4)	1318(88.9)	1.00
1(9.2)	6(9.1)	136(9.2)	1.12
2(2.1)	3(4.5)	29(1.9)	2.39
Husband has other wife			
None (66.5)	24(36.4)	1006(67.8)	1.00
1(5.6)	1(1.5)	86(5.8)	0.49
2(0.8)	1(1.5)	11(0.7)	3.81
No answer (27.1)	40(60.6)	380(25.6)	–
Rank order as wife			
First (58.7)	19(28.8)	890(60.0)	1.00
Second (10.4)	6(9.1)	156(10.5)	1.80
Third or higher (3.7)	1(1.5)	56(3.8)	0.84
No answer (27.2)	40(60.6)	381(25.7)	–

Use of Contraceptives

Slightly less than half (48.0%) of the sample had used or were using some form of contraceptive at the time of the interview. Contraceptive pills were the most common form, and intrauterine devices were used by 9.6% of the respondents, while other forms of contraceptives were rarely used by the Saudi women.

Comparison of the results of HSV-2 antibody investigation did not show significant difference between the groups of contraceptive users and nonusers (Table 6), although the contraceptive users had slightly higher positive results of HSV-2 antibodies than the nonusers.

TABLE 5. *Distribution of pregnancy patterns among seropositive and seronegative Saudi women.*

	HSV-2 antibody		
Pregnancy pattern (% of study sample)	Positive (n=66) No. (%)	Negative (n=1483) No. (%)	Risk ratio
No. of pregnancies			
⩾ 5 (32.5)	23(34.8)	481(32.4)	1.00
3 – 4 (20.0)	10(15.1)	300(20.2)	0.70
1 – 2 (35.8)	10(30.3)	535(36.1)	0.78
Never pregnant (11.3)	13(19.7)	162(10.9)	1.68
No answer (0.3)	0	5(0.3)	–
History of miscarriage			
Yes (30.4)	17(25.8)	454(30.6)	1.00
No (57.8)	36(54.5)	860(58.0)	1.12
Never pregnant (11.3)	13(19.7)	162(10.9)	2.14
No answer (0.5)	0	7(0.5)	–
History of abortion			
Yes (3.2)	2(3.0)	48(3.2)	1.00
No (85.3)	51(77.3)	1271(85.7)	0.96
Never pregnant (11.3)	13(19.7)	162(10.9)	1.93
No answer (0.1)	0	2(0.1)	–

TABLE 6. *Distribution of contraceptive use among seropositive and seronegative Saudi women.*

	HSV-2 antibody		
Use of contraceptive (% of study sample)	Positive (n=66) No. (%)	Negative (n=1483) No. (%)	Risk ratio
Use of contraceptives			
No (51.5)	32(48.5)	766(51.6)	1.00
Yes (48.0)	34(51.5)	710(47.9)	1.15
No answer (0.5)	0	7(0.5)	–
Use of pills			
No contraceptives (51.5)	32(48.5)	766(51.6)	1.00
Pills (44.8)	30(45.5)	664(44.8)	1.08
Other contraceptives (3.0)	3(4.5)	44(3.0)	1.63
No answer (0.6)	1(1.5)	9(0.6)	–
Use of IUD			
No contraceptives (51.5)	32(48.5)	766(51.6)	1.00
IUD (9.6)	7(10.6)	141(9.5)	1.19
Other contraceptives (38.2)	27(40.9)	565(38.1)	1.14
No answer (0.7)	0	11(0.7)	–

Discussion

Our study was a cross-sectional survey of marital and coital variables and socioeconomic characteristics with regard to the risk of infection with HSV-2 among Saudi women who attended the gynecology clinic at the King Khalid University Hospital for various gynecologic complaints from September 1983 to March 1988.

The 1549 sampled Saudi women included in the survey were selected primarily to examine the effect of socioeconomic and marital variables on the risk of infection with HSV-2, and not to estimate HSV-2 prevalence among Saudi women.

The study results indicated that 4.3% of the women had HSV-2 seropositivity and that there were relatively more women with positive HSV-2 antibodies among the older age groups. The illiterate women and those who lived in poor housing conditions also showed a higher rate of HSV-2 seropositivity. On the other hand, respondents who belonged to the upper income group had relatively higher HSV-2 seropositivity than the lower income group.

Other serologic surveys had indicated that the maximum occurrence of HSV-2 seropositivity was reached by the ages of 35 and 50 years in most of the population sampled and have demonstrated a correlation between socioeconomic status and the occurrence of antibodies to HSV-2.[2,10,11] The results of the present study suggested that women whose husbands were in the upper occupational categories had a relatively higher risk of HSV-2 seropositivity. Also, the women whose husbands had traveled abroad during the past 12 months were at more risk. Among this group, those women whose husbands had traveled to Europe, North America, and Africa were prominently associated with higher risk ratios.

The data further showed that the youngest age group (less than 15 years) had slightly higher risk ratios than the older groups. However, those women who married for the first time and had their first coitus between the age of 15 and 20 years had lower risk of having positive HSV-2 antibodies.

The women who were married more than twice and the women whose husbands had two or more other wives were at higher risk; their risk ratios were 2.39 and 3.81, respectively. In this regard, the second ranked wives had higher risk of HSV-2 seropositivity. Other studies have also reported that early age at first intercourse and many partners carried an increased risk of HSV-2 seropositivity.[1,5,12-14] A study conducted on black women of lower social class with breast cancer found risk ratios of 2.4 and 3.3 for seropositivity for early age at first intercourse and multiple partners, respectively.[5] However, these relationships between sexual behavior and HSV-2 seropositivity have not been found consistently in all studies of lower social class females. For example, early age at first intercourse was not associated with an increased risk of seropositivity among Ugandan females; however, the occurrence of HSV-2 antibodies detected by microneutralization was very high in this population.[15]

The study further disclosed that the women who had never become pregnant had relatively higher risk of seropositivity than those who had history of pregnancy, miscarriage, and abortion. Among those who had pregnancy records, the respondents with five or more past pregnancies were more at risk than those with fewer number of previous pregnancies. In addition, the data did not show significant difference between the groups of contraceptive users and nonusers, although the contraceptive users had slightly higher positive results of HSV-2 antibodies than the nonusers. To our knowledge, there are no previous reports of these associations in other studies.

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References

1. Adam E, Kaufman RH, Melnick JL, et al. Seroepidemiologic studies of herpesvirus type 2 and carcinoma of the cervix. III. Houston, Texas. Am J Epidemiol 1973;96:427-42.
2. Rawls WE, Campione-Piccardo J. Epidemiology of herpes simplex virus type 1 and 2 infections. In: Nahmias AJ, Dowdle WR, Schinazi RE, eds. The human herpesviruses: an interdisciplinary perspective. New York: Elsevier, 1981:137-52.
3. Rawls WE, Gardner HL, Flanders RW, et al. Genital herpes in two social groups. Am J Obstet Gynecol 1971;110:682-9.
4. McDonald AD, Williams MC, West R, et al. Neutralizing antibodies to herpesvirus types 1 and 2 in Montreal women. Am J Epidemiol 1974;100:124-9.
5. Adam E, Sanders EK, Melnick JL, et al. Antibodies to herpesvirus type 2 in breast cancer and cervical cancer patients. Cancer 1974;33:147-52.
6. Gart JJ. Approximate confidence limits for the relative risk. J R Stat Soc B 1962;24:454-63.
7. Fraser C, Melendez LV, Simeone T. Specificity differentiation of herpes simplex virus types 1 and 2 by indirect immunofluorescence. J Infect Dis 1974;130:63-6.
8. Johnson LD, Fuccillo DA, Stalder H, et al. Comparison of indirect hemagglutination and indirect immunofluorescence tests with microneutralization tests for detection of type—specific Herpesvirus hominis antibody. J Clin Microbiol 1979;9(3):384-90.
9. Ballew HC, Lyerla HC, Forrester FT. Laboratory methods for diagnosing herpesvirus infections: course no. 8229-C. Atlanta, GA: Centers for Disease Control, Bureau of Laboratories, Virology Training Branch, 1979:120-4.
10. Rawls WE, Clarke A, Smith KO, et al. Specific antibodies to herpes simplex virus type 2 among women with cervical cancer. In: Essex M, Todaro G, Zur Hausen H, eds. Viruses in naturally occurring cancers. CSH conference on Cell Proliferation. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1980;7:117-33.
11. Rawls WE, Gardner HL, Kaufman RL. Antibodies to genital herpesvirus in patients with carcinoma of the cervix. Am J Obstet Gynecol 1970;107:710-6.
12. Graham S, Rawls W, Swanson M, et al. Sex partners and herpes simplex virus type 2 in the epidemiology of cancer of the cervix. Am J Epidemiol 1982;115(5):729-35.
13. Rawls WE, Garfield CH, Seth P, et al. Serological and epidemiological considerations of the role of herpes simplex virus type 2 in cervical cancer. Cancer Res 1976;36:829-35.
14. Stavraky KA, Rawls WE, Chiavetta JA, et al. Sexual and socioeconomic factors affecting the risk of past infections with herpes simplex virus type 2. Am J Epidemiol 1983;118(1):109-21.
15. Adam E, Sharma SD, Zelgler O, et al. Seroepidemiologic studies of herpesvirus type 2 and cancer of the cervix. II. Uganda. J Natl Cancer Inst 1972;48:65-72.

ROUTINE OR SELECTIVE ANTIBIOTIC PROPHYLAXIS IN BILIARY SURGERY

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تم استقصاء النبيت الجرثومي المراري لدى مئتين وتسعة وتسعين مريضا ادخلوا الى المستشفى لاستئصال المرارة. ولم يسبق لأى منهم ان عولج بالمضادات الحيوية قبل أخذ عينات الصفراء. كانت نتائج الزرع ايجابية لدى ٨٩ مريضا (٣٠٪) وقد تم عزل عضويات هوائية منفردة لدى ٩٠٪ منهم. وكان معدل التهاب الجرح أعلى بكثير لدى المجموعة ايجابية الزرع كما حصلت الاختلاطات الخطيرة عقب الجراحة لدى مرضى هذه المجموعة فقط. ولترشيد استخدام المضادات الحيوية الوقائية لدى مرضى استئصال المرارة وتحديد مجموعات مرضى الخطر، فقد ربطنا بين نتائج الزرع الايجابية للمرارة وبين عوامل سريرية وكيميائية حيوية واشعاعية معينة كالتهاب الأوعية الصفراوية أو توسع القنوات الصفراوية أو داء السكري أو سن المريض. ثم خلصت الدراسة الى وجوب استخدام المضادات الحيوية وقاية ندى من يحملون عاملا واحدا أو عاملين من عوامل الخطورة التي تمت دراستها. إن اتباع هذه الخطة يحمي نسبة ٨٢٪ من المرضى المعرضين للخطر بينما يجنب نسبة ٧٠٪ من ذوي الصفراء العقيمة من آثار تلقي المضادات الحيوية دونما ضرورة.

The microbial flora of the bile were prospectively studied in 299 patients admitted for biliary surgery. None of those patients received any antibiotic before the bile specimens were obtained. Positive bile cultures were found in 89 patients (30%). Aerobic organisms alone were isolated in 90% of those patients. The incidence of wound infection was significantly higher in the positive bile culture group, and serious postoperative complications occurred only in this group. To rationalize the use of prophylactic antibiotics in biliary surgery and to identify the groups of patients at risk, we correlated the positive bile cultures with certain clinical, biochemical, and radiologic factors such as presence of cholangitis, dilatation of biliary ducts, diabetes, and age. The study concluded that prophylactic antibiotics should be administered to patients with one or more of the risk factors studied. This policy protects 82% of the patients at risk and spares 70% of the patients with sterile bile from receiving antibiotics unnecessarily.

Infection is one of the serious complications of biliary surgery and contributes significantly toward higher morbidity and mortality rates.[1] The reported incidence of bacterial presence in the biliary tract ranges from 8% to 42%.[2-4] The reasons for this wide variation include differences in the methods used to obtain the bile, the culture techniques, and the preoperative use of antibiotics.

Mason, in a study of 100 consecutive cases of biliary surgery, found positive cultures in more than a third, and the majority of cultures showed gram-negative bacteria.[5] Scott found a higher incidence of infected bile in the cases associated with biliary obstruction and drew the attention to the gram-negative bacteremia in such patients.[6] The

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incidence of positive bile cultures increases with age, and the bile may be infected in up to 80% of the patients with acute cholecystitis.[7,8]

A prospective study was undertaken in this hospital to determine the incidence of infected bile in the patients admitted for biliary surgery. None of those patients was thought to have received prophylactic antibiotics before the bile specimen was obtained or during the 2 to 3 weeks before admission.

The bacteriologic data are correlated with various clinical, biochemical, and radiologic observations to identify a group of patients at high risk and to rationalize the use of antibiotics in such patients.

Patients and Methods

Four hundred consecutive patients were admitted for biliary surgery during the period January 1983 to December 1984. Only 32 patients (8%) required emergency surgical intervention, i.e., within 6 to 8 hours of their admission to the hospital. The remaining patients underwent surgery on an elective or semielective basis.

Specimens of bile were obtained during surgery from the gallbladder and/or the common bile duct. When percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography with nasobiliary drainage was performed preoperatively, a specimen of the bile was taken for bacteriologic studies. The specimens of bile were sent to the microbiology laboratory for immediate processing (usually within 30 minutes). All specimens were Gram stained and cultured aerobically and anaerobically. Aerobic cultures were performed in blood agar and MacConkey medium, while anaerobic cultures were carried out in cooked meat broth and in glycolate medium with the Gaspak anaerobic system.

None of the patients was supposed to have received prophylactic antibiotics before the bile specimen was obtained, nor should they have received antibiotics before admission to the hospital.

During the postoperative period, patient progress and complications were documented, and as required, blood was obtained for culture and/or culture swabs were taken from the wounds and drain sites.

Results

During analysis of the data, 101 patients were found to have received some sort of antibiotic before the bile specimen was taken. Those patients were excluded from the study, leaving data from 299 patients to make the core of this study, which fortunately included the group of 32 patients who underwent emergency surgery.

Positive bile cultures were found in 89 patients (30%) (Table 1). A total of 154 organism types were isolated. Gram-negative organisms alone were isolated in 67 patients (75%), gram-positive organisms alone in 13 patients (15%), and a mixture of gram-negative and gram-positive organisms in the remaining nine patients (10%) (Table 2). Aerobic organisms were grown from the bile of 80 patients (90%), anaerobic organisms from three patients (3%), and a mixture of both from six patients (7%).

TABLE 1. *Results of bile culture in 299 patients.*

Category of surgery	No.	Positive culture No.(%)	Negative culture No.(%)
Emergency	32	24(75)	8(25)
Elective/semielective	267	65(24)	202(76)
Total	299	89(30)	210(70)

TABLE 2. *Bacteriology of organisms isolated from 89 patients.*

Type of organisms	No. of patients (%)
Gram-negative	67(75)
Gram-positive	13(15)
Mixture of gram-positive and gram-negative	9(10)
Aerobic	80(90)
Anaerobic	3(3)
Mixture of aerobic and anaerobic	6(7)

Patients over 50 years old had twice as many positive bile cultures as younger patients. The positive bile culture rate was 68% in the patients with acute cholecystitis and rose to 88% in the patients who were jaundiced on admission or gave a history of recent attack of jaundice. Patients admitted with cholangitis or a history of recurrent cholangitis within 2 weeks prior to admission who did not receive antibiotic treatment showed 100%

positive bile culture rate. Ultrasound examination detected a group of patients with distended gallbladders or dilated bile ducts, and those showed positive bile culture rates of 58% and 75%, respectively. Diabetic patients showed significantly higher positive bile culture rate than the nondiabetics (Table 3).

Table 3. *Influence of various factors on the incidence of positive bile culture.*

Factor	No. of patients	Patients with positive bile culture (%)
Age (y)		
⩾ 50 years	92	44(48)
< 50 years	207	46(22)
Jaundice or recent history of jaundice		
Present	43	38(88)
Absent	256	59(23)
Cholangitis or recent history of recurrent cholangitis		
Present	30	30(100)
Absent	269	62(23)
Distention of galbladder		
Present	38	22(58)
Absent	261	68(26)
Dilatation of bile ducts		
Present	44	33(75)
Absent	255	59(23)
Diabetes mellitus		
Present	39	28(72)
Absent	260	67(26)

The wound infection rate was significantly higher in the bile culture positive group as compared to the bile culture negative group, 13% and 4%, respectively.

Eighty percent of the swab cultures from the infected wounds in the positive bile culture group showed the same type of organisms as in the bile. Postoperative complications, such as septicemia, cholangitis, abscess formation, and acute renal failure, occurred only in the positive bile culture group (Table 4).

Two deaths occurred in the positive bile culture group due to overwhelming sepsis, giving a mortality rate of 2% as compared to only one death (0.5%) due to pulmonary embolism in the negative bile culture group. The overall mortality rate among both groups was 1%.

Table 4. *Postoperative morbidity and mortality rates.*

Type of complication	Positive bile culture patients (n=89) No. (%)	Negative bile culture patients (n=210) No. (%)
Wound infection	12(13.0)	9(4.00)
Septicemia	10(11.0)	0
Cholangitis	5(6.1)	0
Intra-abdominal abscess	4(4.5)	0
Renal failure	3(3.0)	0
Death	2(2.0)	1(0.47)

Discussion

We know that patients with positive bile culture are more liable to develop septic complications such as wound infection, septicemia, or cholangitis.[9] Such septic complications do increase the morbidity and mortality rates of biliary surgery.[1] However, many investigators have shown that prophylactic use of antibiotics in biliary surgery can markedly reduce the incidence of such septic complications.[10,11]

In our series we have found that the incidence of infected bile and microbial flora is comparable to other published data.[4,5] As well, the incidence of wound infection was more than three times higher in the positive bile culture group, and serious septic complications such as septicemia, cholangitis, renal failure, and intra-abdominal abscess formation had occurred only in the positive bile culture group. However, if we administered antibiotics prophylactically to all patients undergoing biliary surgery, approximately two thirds of the patients with sterile bile would receive antibiotics unnecessarily (Table 1). This will increase the possibility of antibiotic-resistant strains.[12] Furthermore, with the ever-increasing cost of new antibiotics, it may constitute a significant burden on the budget of health services in developing countries.

In this study we have attempted to identify a group of patients at high risk by studying certain clinical, biochemical, and radiologic factors (Table 3). Some of these factors were studied in detail by other workers.[13,14]

All patients admitted with cholangitis or who had a recent history of cholangitis gave positive bile cultures, while the bile was positive for culture in 88% of the patients admitted with jaundice alone.

Distention of the gallbladder with or without dilatation of the biliary ducts signifies stasis of bile and is associated with high incidence of infected bile, as shown in Table 3. Diabetes mellitus appears to be a common associated illness affecting 39 (12%) of our patients; 28 (72%) of those patients showed positive bile culture. Age above 50 years seems to be another important factor associated with higher incidence of positive bile culture in 48% of the patients as compared to 22% of the patients under the age of 50 years.

If we were to administer prophylactic antibiotics to a group of patients who demonstrate one or more of the factors studied (Table 5), we would cover 82% of the patients in the positive culture group. But, at the same time we would have given prophylactic antibiotics unnecessarily to 30% of the patients with negative bile culture. This compares favorably with the policy of antibiotic cover for all patients undergoing biliary surgery, should blind therapy be applied. By this selection of patients with one or more factors, more than half of the patients (54%) receiving prophylactic antibiotics would benefit from it (Table 6). If two or more factors are taken into consideration, it would include 56% of patients in the positive bile culture group and only 6% in the negative bile culture group with overall benefit for 81% of the patients receiving prophylactic antibiotics. When selecting patients with only three or more positive factors for antibiotic prophylaxis, one would virtually exclude completely all the patients with negative bile cultures from receiving antibiotics, but at the same time, such policy deprives the majority of the patients (68%) with positive bile cultures from receiving prophylactic antibiotics. Therefore, for prophylaxis we propose administration of a single dose of appropriate antibiotic to patients with one or more of the factors studied. Such policy will cover 82% of the patients with infected bile and 30% of the patients with sterile bile. In other words, this policy will spare 70% of the patients with sterile bile from receiving unnecessary antibiotic prophylaxis but also will leave 18% of the patients with infected bile without antibiotic prophylaxis.

In this study the majority of serious postoperative complications (Table 4) occurred in patients with three or more positive factors. Thirty patients belonged to this category, and 29 (97%) of them had positive bile cultures. In more than half of those patients the bacterial flora of the bile and the antibiotic sensitivity were known to us prior to surgery, since we obtained the bile specimens through percutaneous drainage of the biliary tree or through retrograde endoscopy of the biliary system with nasobiliary drainage which were used as methods of investigation or therapy to decompress the biliary system.

In view of the life-threatening complications which are liable to occur in these patients, we feel that in these situations antibiotics should be used therapeutically rather than prophylactically. However, further prospective studies are needed to evaluate whether such a policy would reduce the above-mentioned complications.

TABLE 5. *Correlation between bile culture results and factors studied.*

No. of positive factors	Patients with positive bile culture (n=89)	Patients with negative bile culture (n=210)
One factor or more present	73(82)	62(30.0)
Two factors or more present	50(56)	13(6.0)
Three factors or more present	29(32)	2(0.4)

TABLE 6. *Patients who would benefit from antibiotic prophylaxis.*

Category/ total	Bile culture positive patients No. (%)	Bile culture negative patients No. (%)	% of patients to benefit from antibiotic prophylaxis
No factors present, n=164	15(9)	149(91)	9
One or more factors present, n=135	73(54)	62(46)	54
Two or more factors present, n=63	50(79)	13(21)	81
Three or more factors present; n=30	29(97)	1(3)	95

References

1. Cox JL, Helfrich LR, Pass HI, et al. The relationship between biliary tract infection and postoperative complications. Surg Gynecol Obstet 1978;146(2):233-6.

2. Anderson RE, Priestly JT. Observation of bacteriology of choledochal bile. Ann Surg 1951;133:486-9.
3. Flemma RJ, Flint LM, Osterhout S, et al. Bacteriologic studies of biliary tract infection. Ann Surg 1967;166:563-72.
4. Engstrom J, Hellstrom K, Hogman L, et al. Microorganisms of liver biliary tract and duodenal aspirates in biliary diseases. Scand J Gastroenterol 1971;6:177-82.
5. Mason GR. Bacteriology and antibiotic selection in biliary tract surgery. Arch Surg 1968;97:533-7.
6. Scott AJ. Bacteria and disease of the biliary tract. Gut 1971;12:487-92.
7. Watson JF. The role of bacterial infection in acute cholecystitis: a prospective clinical study. Milit Med 1969;134:416-26.
8. Keighley MRB. Infection and the biliary tree. Clin Surg Int 1982;5:219-35.
9. Keighley MR, Lister DM, Jacob SI, et al. Hazards of surgical treatment due to microorganisms in the bile. Surgery 1974;75:578-83.
10. Keighley MR, Baddeley RM, Burdon DW, et al. A controlled trial of parenteral prophylactic gentamicin therapy in biliary surgery. Br J Surg 1975;62(4):275-9.
11. Morran C, McNaught W, McArdle CS. Prophylactic co-trimoxazole in biliary surgery. Br Med J 1978;2(6135):462-4.
12. Altemeier WA, Cutbertson MR, Vetta M. Prophylactic antibiotic therapy. Arch Surg 1956;71:2-6.
13. Keighley MR, Flinn R, Alexander-Williams J. Multivariate analysis of clinical and operative findings associated with biliary sepsis. Br J Surg 1976;63(7):528-31.
14. Dixon JM, Armstrong CP, Duffy SW, Davies GC. Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients. Gut 1983;24(9):845-52.

THYROID GLAND DYSHORMONOGENESIS: A REPORT OF FIVE CASES WITH A REVIEW OF THE LITERATURE

Abdulrahman Al-Nuaim, FRCP(C); Riad Sulimani, FRCP(C);
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خلل الإنتاج الهرموني للغدة الدرقية هو خلل (خلقي) في الاستقلاب الدرقي. وقد وصفت عيوب متنوعة، ونعرض في هذه المقالة النتائج السريرية والمخبرية والشعاعية لخمسة مرضى يعانون من خلل الإنتاج الهرموني الدرقي ناتج عن عيب في التعضي، كان مترافقًا لدى اثنين منهم بصمم حسي عصبي (متلازمة بندرد)، كما نعرض أيضًا مناقشة للعيوب المختلفة مع التركيز على عيب التعضي.

Thyroid gland dyshormonogenesis is an inborn error of thyroid metabolism. Variable defects have been described. We present clinical, laboratory, and radiologic data of five patients with thyroid dyshormonogenesis due to organification defect; two of them were associated with sensorineural deafness (Pendred's syndrome). Discussion of different defects is included with emphasis on the organification defect.

Inborn errors of thyroid metabolism presenting with goitrous hypothyroidism or euthyroidism may result from partial or complete defect at any stage of thyroid hormone synthesis. These are genetically determined inheritable diseases,[1] believed to be autosomal recessive.

Five cases of thyroid dyshormonogenesis are described. Their mode of presentation, biochemical and radiologic data, as well as different defects that may be encountered in thyroid hormone synthesis are discussed.

Patients and Methods

In 1988, five patients were diagnosed as having thyroid gland dyshormonogenesis. They were referred to the endocrinology clinics for assessment of goiter (five patients), symptoms suggestive of hypothyroidism (one patient), and deafness and mutism (two patients). Thyroid function tests were done by the radioimmunoassay method using commercially available kits. Quality control of the assays was monitored by the Middle East extended quality assessment scheme (MEEQAS) in Riyadh. Antithyroid antibodies were done using the hemagglutination method.

Perchlorate discharge test was performed after oral administration of 100 to 200 μCi of radioactive iodine 123 (^{123}I). Using a scintillation probe and scaler, 1- and 2-hour thyroid uptake was determined followed by a 1-g oral dose of potassium perchlorate. Thyroid uptake was subsequently measured every 15 minutes for 1 hour and every 30 minutes for an additional 1 hour. Each uptake after perchlorate administration was compared with the 2-hour uptake, and the test was considered positive if a drop of 20% or more was obtained.

Technetium 99m scan was performed initially for assessment of enlarged thyroid.

Results

The clinical, biochemical, and radiologic findings in the five patients with thyroid gland dyshormonogenesis are summarized in Table 1.

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Discussion

Inborn errors of thyroid metabolism were first reported over 80 years ago by Pendred,[2] when he described a patient with inherited goiter, deafness, and mutism.

Thyroid hormone synthesis is a sequential process where circulating iodide is trapped by the thyroid, followed by oxidation of iodide mediated by peroxidase enzyme. Tyrosyl residues are then iodinated within thyroglobulin to make monoiodotyrosine and diiodotyrosine, which through a coupling process form tetraiodotyrosine (T4) and triiodotyrosine (T3). T3 and T4 are stored within thyroglobulin, and hydrolysis of thyroglobulin by protease enzyme leads to release of active hormones. Defects of thyroid hormone synthesis at any stage lead to goiter formation with or without hypothyroidism.

With the advent of accurate means of assessing thyroid function through radioimmune assays, radioactive iodine uptake, and thyroid peroxidase activity and thyroglobulin measurement, detailed classification and identification of these defects have become available.[3] An inherited defect at any step of hormone biosynthesis, whether partial or complete, may result in goitrous hypothyroidism or euthyroidism. Homozygous members of the family usually present with a complete defect and goitrous hypothyroidism, while heterozygous members of the family usually have a partial defect and goitrous euthyroidism.

The five patients described had an organification defect; hence, detailed discussion of organifi-

TABLE 1. *Clinical, biochemical, and radiologic findings in patients with thyroid gland dyshormonogenesis.*

No.	Sex	Age (y)	Nationality	History	Family history	Physical examination	Thyroid function tests*	Thyroid antibodies†	Technetium scan	Perchlorate discharge	Audiometry
1	F	11	Saudi	Goiter for 4 mo, no symptoms of hypothyroidism	Grandmother, sister, case 2	Diffuse goiter, 2 times normal size	T3 2.31 T4 128.7 TSH 8.8	ATG 1/100 AMS 1/100	Increased activity with homogenous distribution	2 h, 20%	Normal
2	F	15	Saudi	Goiter for 2 y, no symptoms of hypothyroidism	As above	Diffuse goiter, 3 times normal size	T3 2.0 T4 114.5 TSH 3.9	Negative	Increased activity with homogenous distribution	2 h, 58%	Normal
3	M	28	Saudi	Goiter for 5 y, deaf-mute since childhood, no symptoms of hypothyroidism	One sister, one cousin, deaf; grandmother, father, goiter	Diffuse goiter, 3 times normal size	T3 1.84 T4 63 TSH 9.8	ATG 1/10 AMS 1/100	Increased activity with homogenous distribution	2 h, 28%	Bilateral sensorineural deafness
4	F	8	Jordanian	Deaf-mute since childhood, goiter noted for 2 w	Daughter of case 5	Diffuse goiter, 2 times normal size	T3 2.31 T4 117.1 TSH 1.7	Negative	Increased activity with homogenous distribution	2 h, 51.7%	Bilateral sensorineural deafness
5	F	30	Jordanian	Symptoms of hypothyroidism for 5 y	No family history of goiter or deafness, except case 4	Pulse, 54/min; pale; delayed reflexes	T3 0.6 T4 16.7 TSH 96	Negative	Increased activity with homogenous distribution (Figure 1)	2 h, 42%	Normal

* Reference intervals for thyroid function tests: T3, 0.8 to 2.3 nmol/L; T4, 54 to 141 nmol/L; thyroid-stimulating hormone (TSH), up to 10 mU/L.

† AMS, antimicrosomal antibody; ATG, antithyroglobulin antibody.

cation defect follows. Other specific defects of thyroid dyshormonogenesis are summarized in Table 2.

Organification Defect

This could be either a quantitative deficiency or a qualitative abnormality of the thyroid peroxidase enzyme.[12,13] Because trapped iodine is not organified and bound to thyroglobulin properly, it can be discharged into plasma with perchlorate, and the perchlorate discharge test can thus be used to diagnose organification defect.

A wide spectrum of clinical presentation of thyroid decompensation is seen with organification defect, depending on whether it is partial or complete.[14] This is evident in our patients where the first four cases were clinically and biochemically euthyroid while the fifth patient was clinically and biochemically hypothyroid.

Pendred's Syndrome

Pendred's syndrome is an inheritable disease with an autosomal recessive pattern of inheritance. It is a variant of an organification defect characterized by small to moderate-sized goiter, as well as clinical and biochemical euthyroidism in most patients. Although the perchlorate discharge test suggests an organification defect, the peroxidase activity appears to be normal.[5]

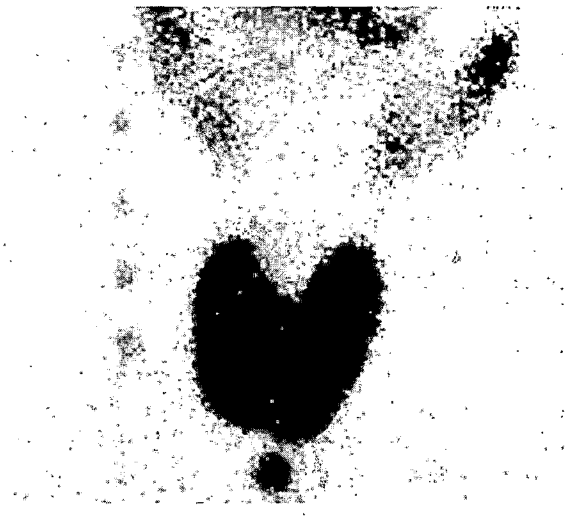

FIGURE 1. Technetium thyroid scan of patient 5 showing increased activity with homogenous distribution.

Pendred's syndrome is associated with congenital sensorineural deafness. The cause of deafness is not clear; since most of patients with Pendred's are euthyroid, hypothyroidism cannot be implicated as a cause of deafness. Patients 3 and 4 had both sensorineural deafness and organification defects. Patients with Pendred's syndrome usually have normal intelligence.

Investigation and Treatment

Organification defect is diagnosed by demon-

TABLE 2. *Possible defects in thyroid gland dyshormonogenesis (other than organification defect).*

Defect	Goiter	T4	Radioactive iodine uptake	Perchlorate discharge	Comments	Therapy
Iodide transport[4,5]	Present	Decreased	Decreased	Normal	No increase in radioactive uptake after exogenous TSH stimulation	Thyroxine
Iodotyrosine coupling[6,7]	Present	Decreased or normal	Increased	Normal	Increased monoiodo- and diiodotyrosine	Thyroxine
Abnormalities of thyroglobulin synthesis with abnormal iodoprotein[8,9,15]	Present	Decreased or normal	Increased	Normal	Simultaneous measurement of thyroxine, iodine by RIA	Replacement with thyroxine when indicated
Iodotyrosine diiodonase[10,11]	Present	Decreased	Increased	Normal	By serum chromatography labeled diiodotyrosine and monoiodotyrosine labeled T3 and T4	Thyroxine

stration of rapid uptake and release of radioiodine and discharge of 15% to 70% of iodide perchlorate, depending on whether the defect is partial or complete. In autoimmune thyroiditis, positive perchlorate discharge test due to intracellular organification defect is seen in approximately 40% of the patients.[16] Thyroid antibodies in our patients were not detectable or positive at very low titers.

Treatment of an organification defect depends on clinical and biochemical findings and the degree of the organification defect judged by the perchlorate discharge test. Patients whose clinical and biochemical findings are in keeping with hypothyroidism tend to have more severe organification defect with high value of perchlorate discharge test, and these patients are treated with thyroxine replacement. Other patients have only goiter with no clinical or biochemical evidence of hypothyroidism, and thyroxine may be given as suppressive therapy for the goiter. Other defects of dyshormonogenesis can be treated by thyroxine as replacement and/or suppressive therapy judged by the clinical and biochemical parameters.

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References

1. Stanbury J, et al. Metabolic basis of inherited diseases. 5th ed. New York: McGraw Hill, 1983.
2. Pendred V. Deaf, mutism, and goiter. Lancet 1896;2:532.
3. Burrow GN, Spaulding SW, Alexander NM, et al. Normal peroxidase activity in Pendred's syndrome. J Clin Endocrinol Metab 1973;36:522-30.
4. Lever EG, Medeiros-Neto GA, Degroot LJ. Inherited disorders of thyroid metabolism. Endocr Rev 1983;4(3):213-39.
5. Medeiros-Neto GA, Bloise W, Ulhoa-Cintra AB. Partial defect of iodide trapping mechanism in two siblings with congenital goiter and hypothyroidism. J Clin Endocrinol Metab 1972;35:370-7.
6. Gavaret JM, Cahnmann HJ, Nunez J. Thyroid hormone synthesis in thyroglobulin: the mechanism of the coupling reaction. J Biol Chem 1981;256(17):9167-73.
7. Morris JH. Defective coupling of iodotyrosine in familial goiters: report of two patients. Arch Intern Med 1964;114:417-23.
8. Kusakabe T. A goitrous subject with structural abnormality of thyroglobulin. J Clin Endocrinol Metab 1972;35:785-94.
9. Riesco G, Bernal J, Sanchez-Franco F. Thyroglobulin defect in a human congenital goiter. J Clin Endocrinol Metab 1974;38:33-41.
10. Kusakabe T, Miyake T. Thyroidal deiodination defect in three sisters with simple goiter. J Clin Endocrinol Metab 1964;24:456-9.
11. Ismail-Beigi F, Rahimifar M. A variant of iodotyrosine-dehalogenase deficiency. J Clin Endocrinol Metab 1977;44(3):499-506.
12. Medeiros-Neto GA, Knobel M, Yamamoto K, et al. Deficient thyroid peroxidase causing organification defect and goitrous hypothyroidism. J Endocrinol Invest 1979;2(4):353-7.
13. Niepomniszcze H, Rosenbloom AL, DeGroot LJ, et al. Differentiation of two abnormalities in thyroid peroxidase causing organification defect and goitrous hypothyroidism. Metabolism 1975;24(1):57-67.
14. Perez-Cuvit, Crigler JR Jr, Stanbury JB. Partial and total iodide organification defect in different sibships in a kindred. Am J Hum Genet 1977;29(2):142-8.
15. Ljunggren JG, Vecchio G. Studies on a patient with congenital deafness, nodular goitre, positive perchlorate test, abnormal biosynthesis of thyroglobulin and a high total concentration of thyroid peroxidase (abstract). Acta Endocrinol 1969;138(suppl):174.
16. Pinchera A, Fenzi GF, Bartalena L, et al. Thyroiditis. In: De Visscher M, ed. The thyroid gland. New York: Raven Press, 1980;413-41.

Special Communication

THE PHARMACIST AS A SOURCE OF DRUG INFORMATION

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Pharmacists have traditionally played an important role as disseminators of drug information.[1,2] The need to provide accurate, unbiased, and up-to-date drug information is becoming ever more important in a world which is experiencing a drug and health information explosion. The pharmacist still remains the most easily accessible health care professional to the general public as well as the medical community and is, therefore, more likely to be the first person approached for drug information. The pharmacists' educational training should, theoretically, make him or her the most qualified member of the health care team to perform this duty.

Drug information needs can vary from requests as simple as drug identification to those as complex as recommendations for patient-specific therapy. The training needed by the pharmacist to fulfill his or her role as a source of drug information depends on the level at which the pharmacist wishes to practice. The ability to provide drug information accurately on these various levels requires, as a first step, the development of skills relating to the collection, storage, retrieval, evaluation, and dissemination of drug information. Relevant academic and practical training in pharmacology, therapeutics, pathophysiology, and clinical pharmacy are the basic foundation in training the pharmacist to become a drug information specialist. It should be emphasized that not all pharmacists should be trained to become drug information specialists, but all pharmacists should be proficient in using basic pharmacologic texts to answer basic drug information queries that relate to drug use, adverse drug reactions, drug compatibility, and so forth.

The dissemination of information can take place in a hospital setting or on the community or national levels. The drug information needs in each setting may vary, but the skills required to provide this information are basically the same. In the context of establishing a drug information service in a hospital, it is necessary first to assess the drug and health information needs of that setting in light of the manpower and reference resources available at hand. It is also important to determine the optimum sites and means of disseminating that information. Although the idea of drug information centers is not new in Saudi Arabia, guidelines will be suggested for establishing the most appropriate drug information service that serves the needs of a particular hospital and for the type of training needed by the pharmacist to play a more active role in providing drug information. A hospital drug information center can affect and contribute to many other important clinical, administrative, and health care areas.

Training the Student Pharmacist

Although all pharmacists play a role in drug information, only those with specialized training or experience or both should practice in a drug information center. Not all pharmacists will become drug information specialists, but all pharmacists have a drug information role. All pharmacists with undergraduate degrees should, at the very least, possess basic skills in retrieving, evaluating, and disseminating drug information. They should be able to handle most requests involving drug formulation, stability, incompatibility, conditions of storage, dosages, methods of administration, drug interactions, contraindications, side effects and toxicity, as well as appropriate therapeutic use. With the additional train-

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ing provided by a drug information residency, these individuals should be able to establish and run drug information centers in small or medium-sized community hospitals. A more in-depth exposure provided by a postdoctoral clinical pharmacy residency program would prepare pharmacists to become drug information specialists and enable them to establish and operate drug information centers in tertiary care or university teaching hospitals.[3]

Laying the appropriate foundation on which to build a cadre of well-trained drug information specialists depends initially on the strength of clerkship or postgraduate residency programs. The curriculum must realistically prepare the pharmacist to be able to handle and resolve real-life clinical situations in both the hospital and community arenas. For this to be possible, a close working relationship between the academic training site (the university) and the practice site (hospital or community pharmacies or clinics) must be developed. The training of the drug information specialist is a stepwise process which begins by ensuring a mastery of the basic sciences as a first step. From that point, the pathophysiology of disease and the pharmacologic basis for the treatment of disease are the next steps. The curriculum is not designed to train the pharmacist to diagnose, but rather to understand the rationale of drug usage in a particular clinical state and also to differentiate between the effects of drugs versus the natural progression of disease states. The mastery of pharmacologic principles along with a sound understanding of the pathophysiology of disease are essential building blocks of clinical pharmacy practice.

Clinical pharmacy is the combined application of these building blocks in a clinical setting. Clinical pharmacy deals essentially with the therapeutic and toxic monitoring of drugs, the application of pharmacotherapeutic and pharmacokinetic principles in drug dosing and usage, as well as researching and evaluating new drug therapies. With a sound clinical pharmacy background, the pharmacist can then specialize in the field of drug information.

Drug Information Residency Programs and a National Drug Information Network

The development of a residency program in drug information, in conjunction with established drug information centers at major medical centers and schools of pharmacy in Saudi Arabia is extremely important. Such a program would greatly contribute to the building of a national core group of drug information specialists. From such a core group, a national drug information network could be developed to provide informational support for practicing health care professionals in hospitals and in the community and organizational support for pharmacists desiring to establish basic drug information services in their areas.

Drug information centers are already in existence in Saudi Arabia and have been since 1975. Unfortunately, most of these centers are not being used to their maximum potential and capacity, and there is much duplication of effort. It would be beneficial for the centers around the Kingdom to establish lines of communication and to share information, experience, and expertise. Such a cooperative venture could eventually result in the formation of a national drug information network. Duplication of effort and wastage of resources could be reduced greatly by closer cooperation and coordination between these centers. As an example, certain computerized drug information resources may be very expensive for one hospital to afford, but such resources are less expensive when they are shared among hospitals.

The concept of national drug information networks is not a new one, and has been applied in various ways by both the US and UK for a number of years.[2,4] Calder et al[2] described the drug information network in the United Kingdom Health Service. The establishment of this network has resulted in less duplication of effort and more rational use of resources in terms of staffing and budget. Moreover, they have been able to develop an extensive data base of literature abstracts, regional specialization in particular drug information subject fields, a code of practice for drug information pharmacists, and publication of specialty bulletins. The establishment of such a network in Saudi Arabia is an achievable and desirable goal, made more relevant by the scarcity of manpower and financial resources.

Community Pharmacists' Role in Drug Information

The community pharmacy in Saudi Arabia, not unlike the community pharmacies of other countries, is predominantly a commercial venture, with the community pharmacist playing a limited clinical role in the dispensing of medications. It is at this level where accurate drug and health information is most needed and where, unfortunately, some abuses of medication usage are taking place.

Any effort to promote and develop the drug information role of the community pharmacist and to ensure that he is disseminating this information accurately will most certainly require the direction and coordination of a national regulatory body such as the Ministry of Health. It is from such a body that a national policy can be formulated and promulgated to ensure professional and educational standards of practice and licensure for pharmacists practicing in the Kingdom.

Community pharmacists can play an important role in patient counseling and should be able to give basic drug information in terms of appropriate drug usage, administration, dosage, side effects, storage, and drug-drug and drug-food interactions. However, it is important that community pharmacists develop an awareness of when a patient needs to be referred to a doctor.

Certain key reference books should be available in every community pharmacy: a drug monograph book, e.g., Martindale's, AHFS Drug Information, Facts and Comparisons; a drug interactions book; a poison management book; a book on drugs in pregnancy and lactation; drug identification books for the Middle East, e.g., MIMS and Medical Index; and a patient counseling book.

Continuing education is an important means for updating pharmacists on new concepts in pharmacy practice, as well as upgrading the standard of pharmacy practice in the country. As many community pharmacists do not have access to information on current developments in drug therapy, it would be desirable to establish mandatory programs for continuing education. Each pharmacist should fulfill a certain number of continuing education credits as a prerequisite to continued licensure in the Kingdom. National symposia on pharmacy-related issues have been conducted by the Ministry of Health and several universities and hospitals. More such symposia need to be encouraged and continued. It is important that community pharmacists have access to these forums of information to expand and update their knowledge base in appropriate pharmacy practice. Issues such as patient counseling and how to use basic drug information references could be reinforced at these symposia.

Establishing Drug Information Services in a Hospital

Before establishing a drug information service in a hospital, it is necessary to evaluate the drug and health information needs of the hospital staff and patient population; assess manpower and reference resources; and determine the optimal sites and means for disseminating drug information.

In a hospital setting, it is important to have knowledge of the patient population being treated and the kinds of services being provided at that hospital. A drug information center should be geared to supporting and strengthening those services. Equipping a drug information center is a step-by-step process and does not occur overnight. Services can be provided with a few key reference books initially and then expanded as other informational resources become available. Ideal manpower and reference sources include a trained drug information specialist and reference sources (such as books, journals, newsletters, abstracting services, microfiche information systems, and computerized information systems). Well-equipped and well-staffed office space with good location is necessary. Furthermore, members of the medical staff who are willing and qualified to provide consultative assistance need to be identified, and the overall support of the hospital administration is essential.

Potential sites and means for disseminating drug information would include, of course, the telephone, pharmacy-published newsletters, memos to staff, in-services to physicians and nurses, physician morning reports, "drug fairs," and drug symposia, and continuing education courses.

At King Faisal Specialist Hospital and Research Centre, the drug information center was established in Ramadan 1406, with the purpose of providing accurate and up-to-date drug and poison information to health care professionals. Its functions also include assisting in the formulation of hospital policy as it relates to drug therapy and usage and participating in medical and clinical pharmacy research both in the hospital and in the Kingdom.

The drug information center is a service provided by the Department of Pharmacy and is located in the main inpatient pharmacy, and a staff member is available around the clock to respond to drug information queries.

The drug information center was introduced to the hospital by advertising its services through hospital memos, nursing in-services, and physician morning reports. Physicians, nurses, and other health professionals were informed as to the type of drug information queries the center was designed to handle, along with the times and means for contacting the center. Pocket-sized pamphlets containing important drug information tables and the office hours and telephone and pager numbers of the center were distributed. Adhesive stickers containing the telephone and pager numbers of the center and its office hours were distributed to all nursing units for placement on telephones.

The center employs one full-time drug information specialist who has advanced training in this field. The informational resources available to the center include the Iowa Drug Information Service microfiche system, the Micromedex computer system, more than 200 medical and pharmaceutical reference books, 18 pharmaceutical journals and newsletters, and two abstracting journal services. In addition, an extensive medical library is also present in the hospital when more in-depth research or computerized literature searches need to be conducted.

For storing information, extensive drug and disease files are maintained on computer and expanded on a regular basis. All pharmaceutical journals and newsletters are reviewed on a monthly basis to identify articles of interest and clinical significance and are entered into the data base. This computer system provides the Pharmacy Department with quick access to recent articles on a particular topic.

The center assists in the formulation of drug policy on a hospital-wide basis and promotes appropiate drug usage through its participation on the Pharmacy and Therapeutics Committee. In addition, the center is responsible for evaluating all new drug requests for formulary addition, as well as any drug-related topics which are raised at the meetings.

The drug information center updates the *Hospital Formulary* on an annual basis. The formulary varies from the traditional format of most hospital formularies in that it contains a listing of commonly used adult dosages next to the generic listing of drugs.

In an effort to promote rational antibiotic drug usage at our hospital, the drug information center was intimately involved on an Antibiotic Working Committee to draft an antibiotic guidelines handbook. The center researched and compiled the initial data for the handbook and coordinated input from more than 35 physician specialists.

The center provides in-service training for medical, nursing, and pharmacy staff on various drug-related and therapeutic topics. These in-services foster a closer working relationship between the pharmacy and departments in the hospital.

The drug information center coordinates the hospital's adverse drug reaction program, which documents the incidence and type of adverse drug reactions occurring at the hospital. This information is reviewed by the Pharmacy and Therapeutics Committee. The center also assists in coordinating and developing criteria for on-going and prospective drug utilization reviews of individual drugs or drug classes. The center has cooperated with several members of the medical staff in conducting and developing protocols for clinically oriented pharmacy research projects. Several of these are in the process of publication.

Plans for the drug information center include the establishment of a post-undergraduate residency program in drug information in conjunction with the King Saud University, School of Pharmacy. It is hoped that such a program would give the pharmacist possessing an undergraduate degree sufficient training to enable him or her to establish and run a drug information center in a small or medium-sized community hospital.

Closer ties among drug information centers in the Kingdom may lead to the establishment of a national drug information network to make the best use of available manpower, as well as informational and financial resources at hand.

Conclusion

There is a need to provide accurate, up-to-date drug information that relates to health care issues relevant to a particular community, region, or hospital in Saudi Arabia. As the pharmacist is the most easily accessible health care professional to the general public, it is vital that this valuable resource person be trained in the appropriate fashion. The promotion and development of the drug information role of the community and hospital pharmacist will require the direction and coordination of a national regulatory body such as the Ministry of Health as well as assistance from established drug information centers and schools of pharmacy within the Kingdom. Policies should be promulgated to ensure minimal professional and educational standards of practice and licensure for all pharmacists practicing in the Kingdom. The design of mandatory continuing education programs and the development of a national drug information network would greatly contribute to the realization of these goals.

References

1. Osol A. Remington's pharmaceutical aciences, 16th ed. Easton, Pa: Mack Publishing Co, 1980.
2. Calder G, Davies JS, McNulty H, et al. Drug information network in the United Kingdom National Health Service. Am J Hosp Pharm 1981;38:663-6.
3. Cardoni AA. Drug information centers: meeting future needs for drug information. Am J Hosp Pharm 1983;40:1215-7.
4. Amerson AB, Wallingford DM. Twenty years experience with drug information centers. Am J Hosp Pharm 1983;40:1172-8.

Case Reports

SPONTANEOUS RUPTURE OF THE KIDNEY: CASE REPORT AND REVIEW OF THE LITERATURE

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Spontaneous rupture of the kidney of nontraumatic origin occurs rarely. The first detailed case was described in 1856 by Wunderlich,[1] and this condition was identified as Wunderlich's disease thereafter for many years. Herein we report a case of spontaneous rupture of the kidney due to underlying arteriovenous malformation. To our knowledge this is the first case reported in Saudi Arabia.

Case Report

A 37-year-old Saudi man presented to the emergency room complaining of sudden onset of abdominal pain, mainly in the right upper quadrant and right flank. The pain started after he returned to bed following his morning prayers. The pain was severe and associated with nausea but no vomiting. He had diarrhea but no fever and denied any history of trauma to the flanks. Two weeks before admission, the patient had complained of headache and said he felt as if his eyes were popping out. He visited his family physician who told him his blood pressure was high, and he was given antihypertensive medications. The patient had gastric surgery 8 years previously for peptic ulcer disease and appendectomy during childhood. A year ago he was told he had high blood pressure and was prescribed antihypertensives, which he took for only 2 weeks.

On examination the patient was in severe distress and was slightly pale. There was no cyanosis, jaundice, or edema. Blood pressure on the day of admission varied from 170/110 to 240/140 mm Hg. Heart rate was 100 beats per minute and regular. Temperature was 37.3°C. Funduscopy showed severe arteriovenous nicking. Heart sounds were normal with a soft systolic murmur. The abdomen was hard with guarding and severe tenderness over the right flank with fullness and ill-defined mass in the right flank. Bowel sounds were present. Genitalia and rectal examination were normal.

Laboratory investigations revealed hemoglobin of 90 g/L and hematocrit of 0.27. Urinalysis revealed microscopic hematuria with 15 to 40 red blood cells per high-power field. There were no casts and 2 to 3 leukocytes per high-power field. Serum electrolyte levels, renal biochemical analysis, and liver enzyme levels were normal. Plain x-ray films of the abdomen showed haziness in the right upper quadrant, and the psoas shadow was obliterated. Intravenous pyelogram indicated good-functioning kidneys bilaterally, and the right ureter was displaced medially. Ultrasound of the kidneys showed right perinephric fluid collection. Computed tomographic scan of the abdomen showed that the right kidney was pushed anteriorly by the perirenal collection of fluid with a wide rupture at the upper pole of the right kidney (Figure 1).

Blood pressure was controlled with increasing doses of hydralazine and propanolol. The patient was transfused with 2 units of packed cells, and after his condition stabilized, he underwent renal angiogram, which indicated an arteriovenous malformation in the right upper pole area and a second one at the site of the rupture. Both malformations appeared to be fed by the same branch of the right superior artery of the right posterior renal artery. There was evidence of arterial narrowing in the main right renal artery as well as in the segmental renal arteries, this finding was compatible with hypertension of some duration.

Electrocardiogram showed changes of left ven-

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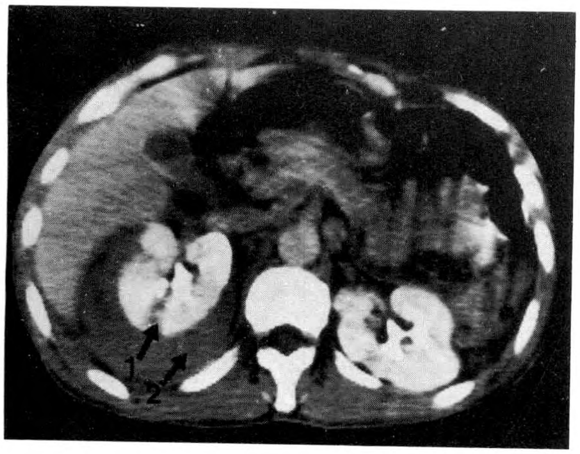

FIGURE 1. Abdominal CT scan with contrast. Arrow 1 indicates rather large rupture of the right kidney. Arrow 2 shows a large, well-encapsulated perirenal collection of fluid (blood).

tricular hypertrophy, and echocardiogram revealed severe concentric left ventricular hypertrophy with well-preserved contractility.

The patient was managed conservatively with antihypertensives, narcotics, and supportive measures. His hospital course was subsequently uneventful, and after 3 weeks, he was discharged on antihypertensive treatment.

After a year of follow-up, the patient has remained well with good control of blood pressure, and repeat CT scan has shown complete resolution of hematoma. After discharge from the hospital, the patient underwent monthly CT scans of the abdomen for 4 months, and by the fourth month, complete resolution of hematoma had occurred. One attempt at angiographic embolization of the remaining arteriovenous malformation in the right upper lobe was unsuccessful because of the technical difficulty of getting the catheter into the right posterior superior branch of the renal artery.

Discussion

Spontaneous rupture of the kidney is exceedingly rare. It is generally believed that in all such cases there is an underlying renal pathology.[7] Approximately 30% of the cases will have a vascular cause such as arteriovenous malformation or aneurysm or diffuse vascular disease.[3,8] Approximately 50 cases of spontaneous kidney rupture in polyarteritis nodosa have been described.[9] Other renal parenchymal diseases, such as glomerulonephritis, pyelonephritis, tuberculosis, neoplasia, hydronephrosis, and renal abscess, have been associated with spontaneous kidney rupture. It is virtually impossible to develop spontaneous kidney rupture in otherwise normal kidneys.

Renal rupture can be defined as an extravasation of blood or urine in the perinephric area. Rupture of the kidney because of trauma is not uncommon, but spontaneous rupture of a kidney is a rare event.[3] About 300 cases have been reported so far in the world literature.[2] Spontaneous rupture of the kidney is usually secondary to an underlying renal parenchymal disease or vascular disease or a coagulopathy. However, one case of spontaneous kidney rupture with no underlying renal disorder has been documented.[3]

The classic presentation of spontaneous rupture of the kidney includes acute severe flank pain, vomiting, diaphoresis, signs of internal hemorrhage, and hypovolemia. Shock may or may not be present, depending on the amount of bleeding. Less often, hypertension may develop due to reduced perfusion of the renal parenchyma resulting in regional ischemia and increasing renin production. Other reported findings include hematuria, elevated temperature, bluish discoloration over the flank, sympathetic pleural effusion on the same side, and paralytic ileus.

None of these findings is pathognomonic, however. Our patient presented with the typical features described by many. He had sudden severe abdominal pain, hematuria, and hypertension. Interestingly, he had a history of symptomatic hypertension for at least a year and did not take his prescribed antihypertensives. For 2 weeks prior to admission and before the kidney rupture he had experienced much more severe headaches. It is plausible that the patient initially had developed hypertension independently or as a consequence of his arteriovenous malformation, which in turn had resulted in nephrosclerotic changes seen on renal angiograms and subsequently rupture of the arteriovenous malformation and the kidney. Nonetheless, the funduscopic finding of severe arteriovenous nicking, left ventricular hypertrophy on ECG, severe concentric hypertrophy of left ventricular wall on echocardiogram, and nephrosclerotic change on renal angiogram all indicate that his hypertension was of long duration and intensity with multiple end-organ damage.

Laboratory data revealed anemia with normal renal and liver function. On intravenous pyelogram, the kidneys appeared normal in size and function, but the right ureter was displaced medially. In contrast, ultrasound indicated a large right perinephric fluid collection, and CT clearly demonstrated wide rupture of the right kidney. Abdominal ultrasound and CT scan are the procedures of choice for diagnosis and management.[4,5]

Opinions vary as to the best mode of therapy for spontaneous rupture of the kidney. Previously, most authors have favored immediate surgical intervention and nephrectomy.[3,6,7] Overall, the mortality rate was high, especially if rupture of the renal capsule had occurred when the patient was managed conservatively. However, we feel that there is now a role for conservative treatment in cases where CT scan indicates that the renal capsule has remained intact, i.e., the hematoma is confined within its boundaries, as in our case. Close monitoring of vital signs and repeated CT scans are necessary components of this approach. From a management point of view, we propose that patients with spontaneous rupture of the kidney be subclassified into two categories, depending on the findings by CT scan: (1) spontaneous rupture of the kidney with intact perirenal capsule and (2) spontaneous rupture of the kidney with ruptured renal capsule. The first category can be managed conservatively whereas the second warrants immediate surgical intervention with evacuation of hematoma and partial or complete nephrectomy. Percutaneous aspiration of hematoma is contraindicated as it may cause further bleeding.

References

1. Wunderlich CA. Handbuch der Pathologie und Therapie, 2nd ed, vol 3, part 3. Stuttgart: Ebner & Seubert, 1856:426-8.
2. Mazuch J, Striez I, Malcek V, et al. Spontaneous rupture of the kidney. Acta Med Hung 1986;43(1):59-65.
3. Nissen HM, Kjar NG. Spontaneous rupture of the kidney. Scand J Urol Nephrol 1976;10(2):173-6.
4. Morettin LB, Kumar R. Small renal carcinoma with large retroperitoneal hemorrhage: diagnostic considerations. Urol Radiol 1981;3(3):143-8.
5. Schaner EG, Balow JE, Doppman JL. Computer tomography in the diagnosis of subcapsular and perirenal hematoma. AJR 1977;129(1):83-8.
6. Martin W, Downs R, Flanigan W. Spontaneous rupture of kidney associated with renal papillary necrosis. Urology 1973;2(3):298-302.
7. Regan JB, Benson RC Jr. Congenital renal arteriovenous malformations. J Urol 1986;136(6):1184-6.
8. Joachim GR, Becker EL. Spontaneous rupture of the kidney. Arch Intern Med 1965;115:176-83.
9. Tocci PE, Lankford RW, Lynne CM. Spontaneous rupture of the kidney secondary to polyarteritis nodosa. J Urol 1975;113(6):860-3.

THE MAYER-ROKITANSKY SYNDROME: DIAGNOSIS AND MANAGEMENT OF A PATIENT

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The Mayer-Rokitansky syndrome consists of vaginal agenesis in association with other mullerian anomalies with or without renal defects. We describe one patient diagnosed and treated at our institution. She had vaginal agenesis, absent uterus, mullerian remnants, normal left ovary, cystic right ovary, and absent right kidney.

Case Report

A 20-year-old woman presented to the gynecology clinic in our hospital in 1983 with a chief complaint of primary amenorrhea and infertility. She also complained of passage of stool and flatus per vagina. At that time, she had been married for 8 years. On questioning, she gave a 1-year history of lower abdominal pain and distention. There was no history of other serious illness.

On physical examination, she was a woman of average build with well-developed breasts and normal axillary and pubic hair. The external genitalia were normal; therefore, she was phenotypically female. However, vaginal examination revealed a blind-ending vagina 3 cm in length with no palpable cervix or uterus on bimanual examination. There was a small rectovaginal fistula.

Her urine was clear and sterile. The hemoglobin level and renal function tests were normal. Ultrasound examination demonstrated absence of the uterus, solitary left kidney, and a mass of low echogenicity measuring 3.7 × 1.9 cm in the right iliac fossa region. Intravenous pyelogram revealed solitary normal-functioning left kidney with compensatory hypertrophy (Figure 1). The ureter and bladder were normal. CT examination of the pelvis confirmed the absence of uterus (Figure 2), and the right pelvic mass was clearly defined (Figure 3) with low density contents.

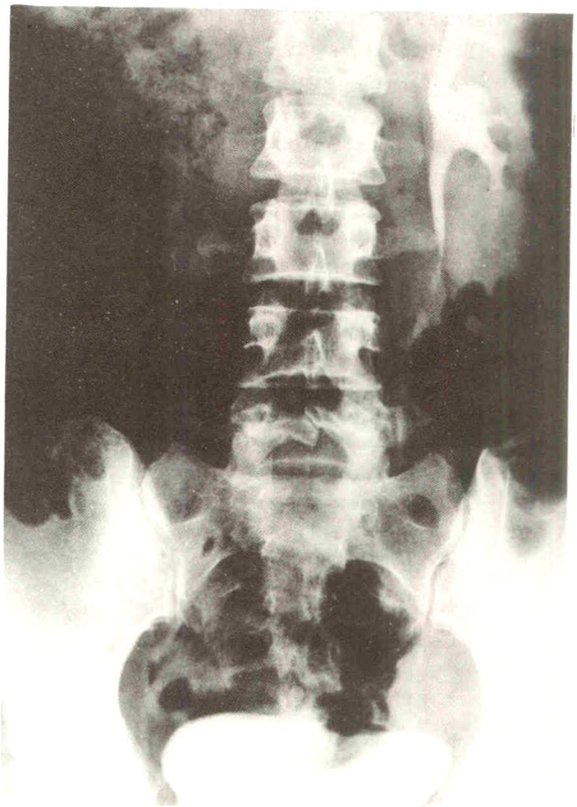

FIGURE 1. Intravenous pyelogram showing solitary left kidney with compensatory hypertrophy.

Buccal smear was positive for Barr bodies. Laparoscopy confirmed absence of uterus, small left ovary, and larger cystic right ovary. Ovarian

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biopsy specimen revealed ovarian stroma enclosing two to three primordial follicles.

The serum levels of follicle-stimulating hormone and luteinizing hormone were normal, and the testosterone level was within the normal range for females. A progesterone challenge test was negative, indicating endocrinologic proof of absent uterine tissues. In July 1983, the rectovaginal fistula was successfully repaired, and the patient made an uneventful recovery.

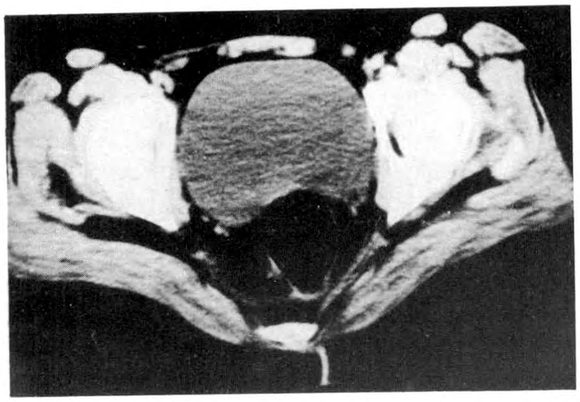

FIGURE 2. CT scan showing absent uterus.

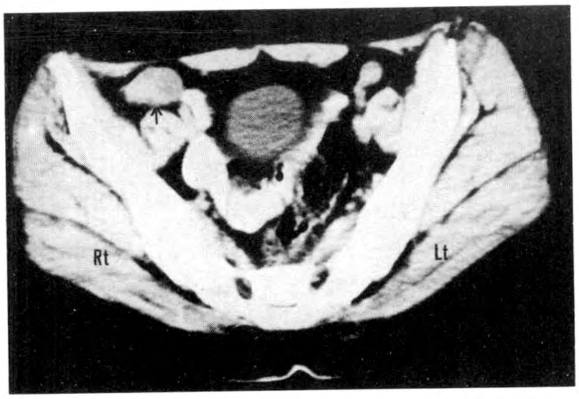

FIGURE 3. Pelvic CT scan showing cyst involving right ovary.

The patient was followed in the outpatient clinic where she complained of marital difficulties due to unsatisfactory sexual intercourse. Vaginoplasty was agreed upon, and a Williams-type operation was carried out in March 1984. Unfortunately, this resulted in a 5-cm-long vagina which was again unsatisfactory. In addition, the patient complained of right-sided abdominal pain.

In October 1987, exploratory laparotomy was carried out. On exploration, the two ovaries were present with a large cyst involving the right ovary. Subsequent histopathologic examination of the excised cyst was reported as corpus luteum. There was a band of tissue in between two short fallopian tubes. Remnants of mullerian ducts were excised. The uterus was absent. The peritoneal reflection from the dome of the urinary bladder lined the blind vaginal pouch and continued over the rectum posteriorly.

A repeat vaginoplasty was conducted by opening this blind pouch. The peritoneal reflection was pulled through and sutured to the vaginal mucosa. The peritoneum over the posterior wall of the urinary bladder was sutured longitudinally and used to form the anterior wall of the neovagina, and the serosal surface of the rectum served as the posterior wall. To reconstruct the vault of the neovagina, we sutured the sigmoid colon across in between the bladder and the rectum to use its serosal surface as a vault, as is done after radical hysterectomy. The neovagina measured 15 cm in length and was constructed over a mold which was removed prior to discharge.

Six weeks after discharge from the hospital, the neovagina maintained its satisfactory length, and only a few fibrinous adhesions were easily broken during digital vaginal examination. At 3 months, the patient was advised to resume sexual intercourse. Finger dilatation was done by the patient up until that time.

Discussion

Aplasia of the uterovaginal canal or the vaginal plate results in complete absence or agenesis of the vagina.[1] The external genitalia and ovaries may be normal since they are not of mullerian origin.[1] Tarry et al[2] have recently defined the Mayer-Rokitansky syndrome as a spectrum of mullerian anomalies, including vaginal agenesis with or without renal anomalies, in genotypic and phenotypic female subjects with normal endocrine status. They have also described the embryologic pathogenesis of this syndrome and proposed a new classification according to the anatomic anomaly (Table 1). In this classification, the letter M refers to mullerian defects. The grades given from 0 to 4 refer to the extent of the mullerian systems affected. Each side is graded individually. According to the classification, the case we are describing is in the M_2M_2 category.

TABLE 1. *Classification of Mayer-Rokitansky syndrome.*

Grade	Description
M_0	Unilateral system normally formed but unfused, or septum retained
M_1	Vaginal agenesis alone
M_2	Vaginal and uterine agenesis
M_3	Total mullerian agenesis
M_4	Mullerian and ovarian agenesis

The same grading number is used to denote the number of anomalies present; e.g., grade 0 is normal except for septal defects; grade 1 has one mullerian (vaginal) anomaly; grade 2 has two (vaginal and uterine) anomalies, and so on.[2]

There was no evidence of ovarian cysts in the series of eight patients described by Tarry et al, all of whom were younger than 20 years of age. However, they stated that the incidence of cysts was 64% in the patients 20 years of age or older. They have also stated that renal ectopy or agenesis occurred in 34% to 43% of patients with Mayer-Rokitansky syndrome. Skeletal anomalies have been reported to occur in 12% of the patients.[3]

In summary, we report one patient with congenital anomalies fulfilling the characteristic features of the Mayer-Rokitansky syndrome. The patient had vaginal and uterine agenesis, short fallopian tubes but normal ovaries, with a cyst involving the right ovary. She also had absence of the right kidney. Initial Williams[4] vaginoplasty resulted in a rather short, unsatisfactory vagina. Since she continued to complain of abdominal pain and lack of complete sexual intercourse, laparotomy was carried out and ovarian cystectomy along with abdominovaginal reconstruction of a long neovagina was achieved.

References

1. Colodny AH. Disorders of the female genitalia. In: Kelalis PP, King LR, Belman AB, eds. Clinical pediatric urology, 2nd ed. Philadelphia: WB Saunders, 1985;2:888.
2. Tarry WF, Duckett JW, Stephens FD. The Mayer-Rokitansky syndrome: pathogenesis, classification and management. J Urol 1986;13(3):648-52.
3. Griffin JE, Edwards C, Madden JD, et al. Congenital absence of the vagina: the Mayer-Rokitansky-Kuster-Hauser syndrome. Ann Intern Med 1976;85(2):224-36.
4. Williams EA. Congenital absence of the vagina: a simple operation for its relief. J Obstet Gynaecol Br Comm 1964;71:511-2.

PLACENTAL MORPHOLOGY IN SIALIDOSIS: REPORT OF A CASE

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Lowden and O'Brien[1] used the term "sialidosis" to describe patients with primary neuraminidase deficiency. According to these authors sialidosis is of two types, type I and type II. In type I, the monomorphic type, patients with juvenile or adult onset have normal mentation or mild mental retardation, cherry-red spots, and myoclonus but are without evidence of dysmorphic features or bony involvement. In sialidosis type II, the dysmorphic type, the patients have Hurler-like features, bony involvement, cherry-red spots, myoclonus, moderate to severe mental retardation, and rapidly progressive clinical course. Type II has been divided further into those with infantile onset and those with juvenile onset.

Infantile sialidosis is the most severe form of sialidosis known and, in fact, the most severe form of lysosomal disease. Affected neonates are born prematurely and have the clinical appearance of hydrops fetalis. They may be stillborn or may survive 1 to 3 months or longer. The diagnosis is based on finding of abnormal sialo-oligosaccharides in the urine and the deficiency of neuramindase in cultured skin fibroblasts.

Case Report

A 32-year-old Saudi woman married to her first cousin was para 7 + 0 (three living children, three died at the age of 30 minutes, 3 months, and 9 months). The last child was diagnosed as having sialidosis. On 12 June 1987, the mother was admitted to the hospital with hydramnios, and ultrasound suggested a severely hydropic baby. On 1 July, no fetal heart sounds were heard, and 2 days later a macerated stillborn female fetus was delivered. The fetus measured 40 cm, and it weighed 1.1 kg. The fetus was not examined and was not investigated for sialidosis. The placenta was delivered completely and weighed 0.77 kg.

Examination of Placenta

Circum-marginate placenta measured 16 × 2 cm, with an eccentrically inserted cord, 30 cm in length. The membranes were dirty-colored, and the cord had three vessels.

The placenta was fixed in formalin and saline, and specimens were embedded in paraffin and stained with hematoxylin and eosin, PAS, and PAS-diastase for light microscopy. Specimens for electron microscopy were taken from formalin-fixed tissue and fixed in 3% glutaraldehyde solution, postfixed in 1% osmium tetroxide solution, and embedded in resin. Semithin sections were stained with lead citrate and uranyl acetate and studied with the electron microscope.

On light microscopic examination, placental villi showed vacuolization of trophoblasts, Hofbauer cells, and placental X-cells. With PAS-diastase stain, the vacuolated cells showed fine PAS-positive granules (Figure 1).

On electron microscopy, most of the vacuolar syncytiotrophoblast and Hofbauer cells of the placental villus showed that their cytoplasm was filled by membrane-bound vesicles, which were mainly translucent and contained fine granules. An occasional vesicle showed incomplete myelin-like bodies (Figure 2).

Discussion

A number of case reports of sialidosis have appeared in the literature.[2-4] Occurrence of these

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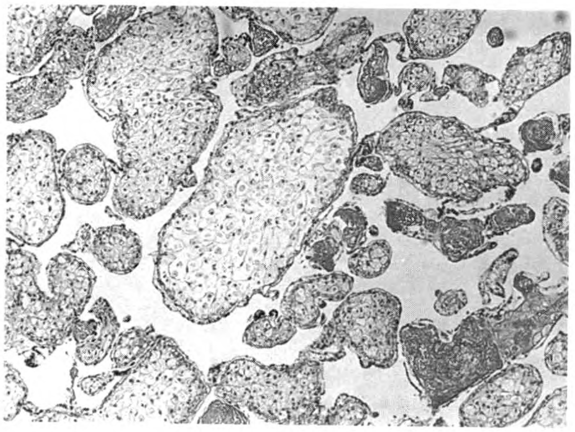

FIGURE 1. Placental villi showing vacuolated cells (hematoxylin and eosin stain, original magnification, ×80).

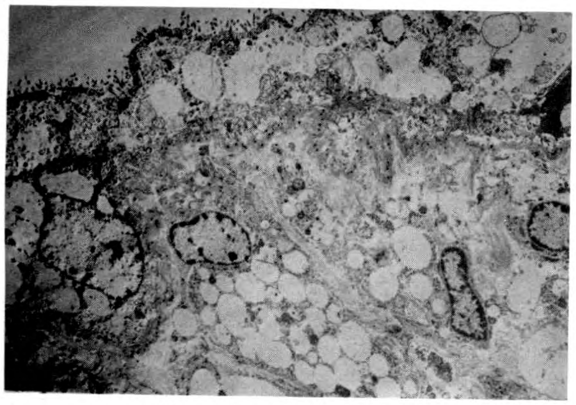

FIGURE 2. Syncytiotrophoblast and Hofbauer cells showing translucent membrane-bound vesicles (original magnification, ×2000).

cases have been described in French, Italian, Japanese, and Portuguese families. To our knowledge, this is the first case report in a Saudi family. Lowden and O'Brien[1] have reported that there is increased incidence of sialidosis in families with consanguineous parents. The parents in this case were cousins.

Aylsworth et al,[2] in their 7-week-old patient with infantile sialidosis, demonstrated vacuoles in the lymphocytes in the peripheral blood and abundant foamy cytoplasm of cells in the bone marrow. The Kupffer cells in the liver biopsy specimen were swollen, and by light microscopy, the liver cells contained large empty vacuoles. The previous child in this family was born at 37 weeks by vaginal delivery, had ascites, hepatosplenomegaly, and vacuolated cells in the peripheral blood. Fibroblast culture and urine examination confirmed the diagnosis of sialidosis.

Although the case under discussion was not investigated further, the history of sialidosis in the family coupled with the presence of vacuolated cells in the placenta strongly point to fetal involvement. Vacuolated syncytiotrophoblast of placenta was described by Lowden et al[5] in their case of GM_1 gangliosidosis. Powell et al[6] studied four placentas and described vacuolated cells in the cytoplasm of placental syncytiotrophoblast and Hofbauer cells. One of their cases was shown to have inclusion cell disease (mucolipidosis II).

Rapola and Aula[7] and Skeles et al[8] described vacuolated cells in the syncytiotrophoblast and Hofbauer cells of placenta studied in mucolipidosis II (I-cell disease) and mucolipidosis IV. Electron microscopic studies performed by these authors have shown that foam cells in the placentas of storage diseases have vacuolar structures containing granular material of low density and sometimes contain membranous inclusions resembling myelin figures or may be clear vacuoles. To our knowledge, no light microscopic or electron microscopic studies have been done in a case of congenital sialidosis.

Since placenta acts as a source of nutrition and exchange of gases between the mother and fetus, it is worthwhile to mention here that extensive vacuolization of placental cells interferes with this important function and hence could be the cause of abortions or stillbirths in these cases of fetal lysosomal storage disorders.

Since in Saudi Arabia placentas are the only material available for study from spontaneous unexplained abortions and stillbirths, this could be of considerable value to elucidate fetal lysosomal storage disorders in this country. These positive findings in the placenta can further alert the clinicians for detailed diagnostic procedures in the future pregnancies.

Acknowledgment

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References

1. Lowden JA, O'Brien JS. Sialidosis: a review of human neuraminidase deficiency. Am J Hum Genet 1979;31(1):1-8.

2. Aylsworth AS, Thomas GH, Hood JL, et al. A severe infantile sialidosis: clinical, biochemical, and microscopic features. J Pediatr 1980;96(4):662-8.
3. Spranger J, Gehler J, Cantz M. Mucolipidosis I: a sialidosis. Am J Med Genet 1977;1:21-9.
4. Stevenson RE, Lubinsky M, Taylor HA, et al. Sialic acid storage disese with sialuria: clinical and biochemical features in the severe infantile type. Pediatrics 1983;72(4):441-9.
5. Lowden JA, Cutz E, Conen PE, et al. Prenatal diagnosis of GMI gangliosidosis. N Engl J Med 1973;288(5):225-8.
6. Powell HC, Benirschke K, Favara BE, et al. Foamy changes of placental cells in fetal storage disorders. Virchows Arch 1976;369(3):191-6.
7. Rapola J, Aula P. Morphology of the placenta in fetal I-cell disease. Clin Genet 1977;11(2):107-13.
8. Skeles E, Ornoy A, Cohen R, Kohn G. Mucolipidosis IV: fetal and placental pathology. Hum Genet 1978;10:47-50.

PULMONARY ALVEOLAR MICROLITHIASIS: REPORT OF FOUR CASES

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Approximately 132 cases of pulmonary alveolar microlithiasis have been reported worldwide, in the United States,[1,2] Europe,[3,4] Africa,[5] South Asia,[6,7] and the Far East.[8] Two cases have been reported from Iraq.[9] This disorder is of unknown etiology characterized by the appearance of tiny intra-alveolar concentrations of calcium salts[10] (mainly of tribasic calcium phosphate[11]). Half of the cases have been in siblings, suggesting some congenital defect in calcium metabolism, although no abnormal biochemical function, has been found.[10] Here, we describe four patients, two of them siblings.

Case Reports

Case 1

A 21-year-old Saudi male, appearing well and active with a moderate build, had a 2-year history of occasional mild dry cough, nonspecific chest pain, and slight blood tinge in sputum. He attributed these symptoms to smoking, which he had started 4 years previously, and smoked 5 to 10 cigarettes daily. He gave no history of fever, dyspnea, weight loss, dysphagia, Raynaud's phenomenon, intermittent claudication, or bladder or bowel disturbances. He had no lymphadenopathy or hepatosplenomegaly. His mother died of pulmonary tuberculosis when he was a child. He gave no history of exposure to birds or dusts (industrial or otherwise). There were no remarkable physical findings other than mild finger clubbing and a few fine crepitations mainly in the infrascapular areas on both sides.

His chest roentgenogram (Figure 1) showed bilateral, extensive, dense, almost calcific fine micronodular shadows involving all lung zones but a little more marked at the bases. Blood analyses including serum calcium level were normal. Blood gases at rest showed a PaO_2 of 12 kPa (90 mm Hg). Tests for LE cells, rheumatoid factor, and antinuclear factor were negative twice. Sputum analysis and culture were negative for pyogenic, fungal, and tuberculous organisms. Electrocardiogram was normal.

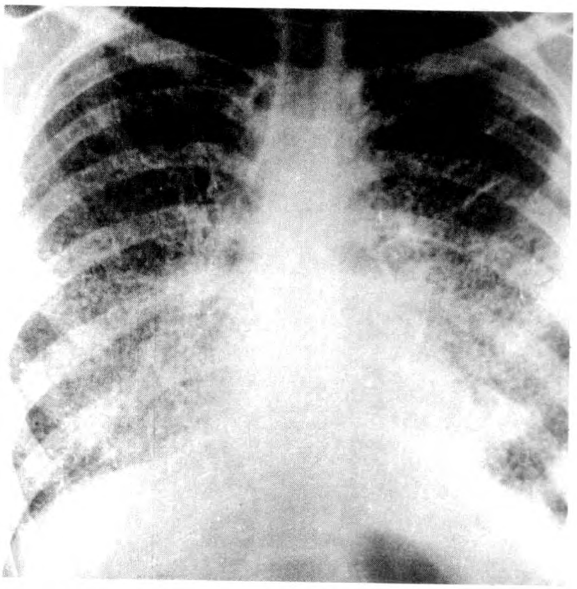

FIGURE 1. Case 1, roentgenogram showing bilateral extensive, high-density, micronodular shadows with some reticulation.

Pulmonary function studies showed primarily a restrictive disorder of moderate degree. Central airway function was normal, but peripheral airways showed quite marked narrowing. The pattern was not suggestive of interstitial lung fibrosis.

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Diffusion studies with carbon monoxide showed a normal carbon monoxide transfer factor with single breath method, but a fall in carbon monoxide transfer factor to about 80% of that predicted with a steady state method. He was subjected to open lung biopsy from the lingula which had a rough feel. The specimen revealed concentrically laminated, rounded, calcified bodies occupying about half the alveoli, which were diagnostic of pulmonary alveolar microlithiasis.

Case 2

A 23-year-old Sıaudi man had a history of dry cough and mild dyspnea (mainly on exertion) for 3 years. He had smoked about 20 cigarettes daily for the past 7 years. For 3 years he had been aware that his chest x-ray film had shown some abnormality, but he failed to pursue evaluation to establish a diagnosis. Nothing else was remarkable about his history except that he had contact with pigeons for the past 6 years. He had no history of industrial or dust exposure. He revealed, however, that his elder sister had recently been found to have a similar chest x-ray abnormality.

On physical examination, he was moderately built, in good general health, not breathless or cyanotic, but he had a moderate degree of finger clubbing. There was no lymphadenopathy or hepatosplenomegaly. He had a few barely detectable, fine, late inspiratory crepitations on deep inspiration heard at both lung bases with equal and fair air entry on both sides. Chest roentgenogram showed bilateral, extensive, almost calcific, very fine micronodulation increasing in density from upper to lower lung zones. Findings on his other clinical investigations (similar to those of case 1) were unremarkable except a tuberculin test (15 mm) to 2 tuberculin units of purified protein derivative.

His pulmonary function tests revealed primarily a restrictive disorder of moderate degree with forced vital capacity (FVC) at 60% of predicted value. Airway function was better than predicted, both at central and peripheral levels, and there was indirect evidence of an increased lung elastance. Thus, it appeared that the restrictive change in this patient was due to the microliths occupying a majority of the alveoli and was possibly enhanced by the development of some changes of interstitial fibrosis in the lungs.

Open biopsy from the lingula, which gave a uniform rough feel, was sent for histopathologic examination. Light microscopy (Figures 2 and 3) revealed a majority of alveoli containing rounded, concentrically laminated calcified bodies (calcospherites). Count of 20 microscopic fields showed approximately 60% of the alveoli involved. The alveolar walls showed fibrous thickening associated with chronic interstitial inflammation which was minimal in some alveoli and moderate in others. Inflammatory cells were predominantly lymphocytes, plasma cells, and macrophages. Eosinophils were not seen in any significant number. These interstitial changes were more often seen around air spaces containing calcospherites. However, no definite relationship was apparent in this regard. These changes probably represent an early stage of interstitial fibrosis and may explain impaired pulmonary function.

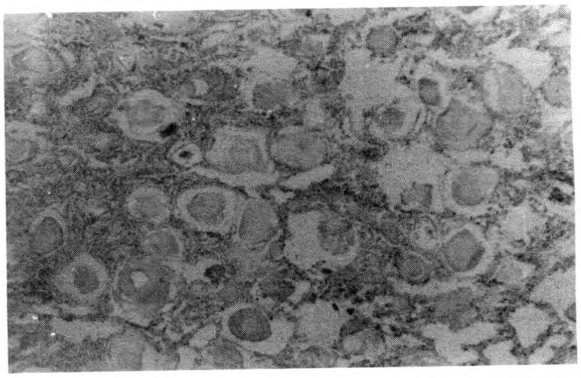

FIGURE 2. Case 2, low-power microscopic view of pulmonary alveolar microlithiasis. Majority of alveoli contain concentrically laminated calcified bodies (calcospherites) (hematoxylin and eosin stain, original magnification, ×40).

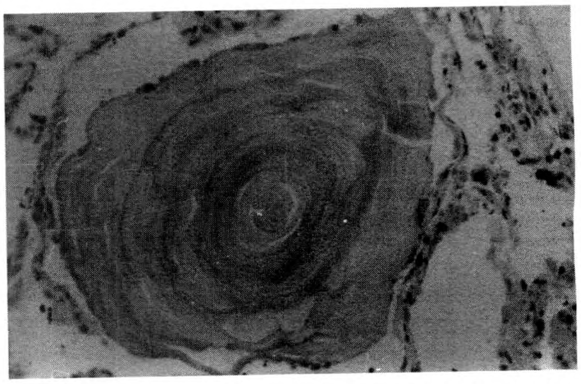

FIGURE 3. Case 2, high-power view of a calcospherite showing typical concentrically laminated structure resembling onion skin (hematoxylin and eosin stain, original magnification, ×400).

Chest roentgenograms of all his family members were taken. His elder sister (case 3) had a similar roentgenographic abnormality.

Case 3

A 26-year-old Saudi woman, full sister of case 2, 3 years earlier had chest x-ray changes similar to her brother's. Her chest roentgenogram revealed bilateral, extensive, dense, fine micronodulation whitening out most of the lung fields, particularly at the bases. She revealed no symptoms, although when asked leading questions, she did admit becoming breathless on moderate to severe exertion. Her dyspnea could be classified as at least grade 1. Her pulmonary function tests revealed a mild restrictive disorder with an FVC of 72% of predicted value. Her resting blood gases revealed a PaO_2 of 12 kPa (90 mm Hg). Physical examination and all other investigations yielded normal results.

Apparently, due to social reasons and her awareness that her abnormality was similar to her brother's, whose diagnosis had been established and no specific treatment had been given except reassurance, she refused to undergo transbronchial or open lung biopsy. Considering the dramatic and specific roentgenographic lung abnormalities in the presence of minimal symptoms and confirmed disease in her brother, we were confident of the diagnosis of pulmonary alveolar microlithiasis.

Case 4

A 15-year-old Saudi boy was referred to our hospital because of radiographic changes in the form of dense bilateral extensive micronodular shadows which were a little more prominent in the middle and lower lung zones as compared to the apices (Figure 4). A similar x-ray abnormality had been observed 1 year earlier. During the past few months, the patient had noticed unusual breathlessness as compared to his friends while doing physical exercise. He had no other symptoms.

On physical examination he showed no abnormal signs. Pulmonary function tests revealed a restrictive disorder of moderate degree with an FVC of 64% of that predicted for him. His airway function was better than predicted, indirectly suggesting increased lung elastance.

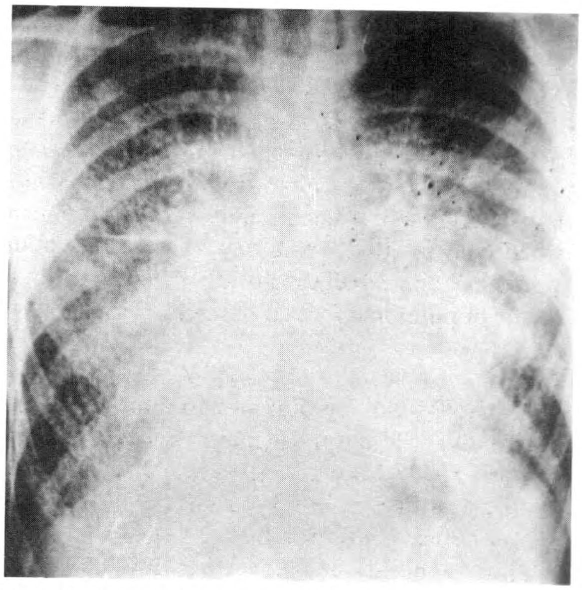

FIGURE 4. Case 4, chest roentgenogram.

A biopsy specimen was taken from the lingula. Histopathology examination revealed concentric, laminated (onion-skin), calcified bodies occupying more than half of the total number of alveoli. The walls of many alveoli showed chronic interstitial inflammation and thickening.

Discussion

Pulmonary alveolar microlithiasis is a rare disorder, and it appears to have no age, sex, racial, or geographic predominance. The age range of patients is from newborn[12] to 80 years, with a mean age at diagnosis of about 35 years.[1] Although the familial occurrence usually affects siblings, occasionally members of successive generations can be affected.[2,13] In our patients the age at diagnosis ranged from 15 to 26 years with a mean of 21 years, and two of four patients were siblings. Like the majority of cases reported elsewhere, the pulmonary function studies of our patients revealed a restrictive pattern, and they had only a few complaints despite widespread radiographic changes. All the cases were diagnosed at a relatively early stage of their illness. This disease progresses slowly, and later on there is increasing dyspnea and cough with little sputum, and later still cyanosis, polycythemia, and cor pulmonale.[14] While some patients' condition may deteriorate in 4 or 5 years,[14] a few have been followed up for more than 30 years without evidence of change.[1] Death, however, occurs in the majority of patients before 55 years of age from respiratory or cardiac failure.[10] No treatment has proved effective.

Although chest x-ray features are fairly specific, transbronchial or open lung biopsy may be done to confirm the diagnosis in a patient with atypical presentation. Histologically, 25% to 80% of the alveoli may contain distinctive concretions which are irregularly concentric, laminated, and often organized around an amorphous central nidus that gives them a typical "onion-skin" appearance.[15] The alveolar walls and interstitium show surprisingly little reaction until late in the course of the disease in the form of septal hypertrophy, cellular infiltrate, or fibrosis.[15] However, in at least two of our patients who were quite young, there was evidence of chronic interstitial inflammation and fibrous thickening of alveolar walls despite the mild symptomatic stage at which they presented to us.

A report on scanning electron microscopy[8] reported that the microliths were globular or irregular in shape or lobulated and in some loci were coalesced. The internal structures consisted of concentric laminar deposits. These findings may imply that the microliths grow by surface deposition and may coalesce during early stages of formation. Elastosis in the alveolar interstitium and deposition of abundant glycogen granules in the bronchiolar epithelial cells were the notable findings of transmission electron microscopy.

In the case of siblings, the chest roentgenogram of the sister (case 3) who was 3 years older than her brother (case 2) showed more dense shadowing; still she did not volunteer significant symptoms, while her brother had had cough and mild dyspnea for 3 years. His smoking may have aggravated his earlier symptoms. His pulmonary function tests did not show any features of airway obstruction, but it is possible to miss early smoker's changes in the presence of some interstitial fibrosis that this patient exhibited on histopathology.

Whenever a patient has dense, extensive, micronodular shadows (especially if they are of almost calcific density), with or without some reticulation progressing downward on chest roentgenogram, in the presence of minimal or no symptoms at all, particularly if any previous chest x-ray film reveals a similar abnormality, pulmonary alveolar microlithiasis should be strongly considered in the differential diagnosis. Other diseases to be considered in the differential diagnosis are sarcoidosis, pneumoconiosis, pulmonary alveolar proteinosis, and diffuse interstitial fibrosis of any etiology including collagen disorder and idiopathic variety. Miliary tuberculosis, not uncommonly seen in this part of the world, is usually differentiated by the fine and discrete micronodularity involving all the lung zones equally and uniformly on the skiagram and, of course, by the patient's symptoms. Even Goodpasture's syndrome and polyarteritis nodosa should be kept in mind, although their clinical features and other organ involvement would be far more obvious. Similarly, a child with idiopathic hemosiderosis may have a diffuse interstitial involvement on chest roentgenogram but be far more symptomatic.

Whenever pulmonary alveolar microlithiasis is suspected or established, all family members of the patient, particularly the brothers and sisters, must be screened with chest roentgenography. That may help to strengthen the diagnosis and also to diagnose more cases, probably at an asymptomatic stage. These patients should be advised to abstain from smoking. There is no cause for panic despite extensive radiographic changes. Reassurance is all that is required. The disorder usually progresses so gradually that the patients adapt themselves and learn, at least in the earlier years of their disorder, to live with their respiratory handicap. As the disorder progresses and complications start to occur, especially in the later stages, attempts should be made to control promptly respiratory infections that may be more frequent and to manage respiratory failure and cor pulmonale that may eventually occur in these patients.

Acknowledgment

The authors thank Dr. Mohammed Al-Mofarreh, Director, Riyadh Central Hospital, and Dr. Mousa Ahmed Bayameen, Director, Taif Chest Hospital, for their interest and encouragement in the preparation of this paper.

References

1. Prakash UB, Barham SS, Rosenow EC 3rd, et al. Pulmonary alveolar microlithiasis: a review including ultra-

structural and pulmonary function studies. Mayo Clin Proc 1983;58(5):290-300.
2. O'Neill RP, Cohn JE, Pellegrino ED. Pulmonary alveolar microlithiasis—a family study. Ann Intern Med 1967;67(5):957-67.
3. Geubelle F, Lambrechts A, Chantraine JM, et al. Pulmonary alveolar microlithiasis: an intestinal (inborn) error? Acta Paediatr Belg 1971;25(2):69-87.
4. Sanz Martin F, Culebras A, Anton T, et al. Pulmonary alveolar microlithiasis: revision of literature in view to two new cases. Bull Inst Med Res Univ Madrid 1965;18(1):35-56.
5. Onadeko BO, Abioye AA, Beetlestone CA, et al. Pulmonary alveolar microlithiasis. Postgrad Med J 1977;53(617):165-7.
6. Thind GS, Bhatia JL. Pulmonary alveolar microlithiasis. Br J Dis Chest 1978;72(2):151-4.
7. Banerjea JC, Mukerji A, Maiti CR. Chronic cor pulmonale due to pulmonary alveolar microlithiasis. Indian Heart J 1967;19(1):47-56.
8. Kawakami M, Sato S, Takishima T. Electron microscopic studies on pulmonary alveolar microlithiasis. Tohoku J Exp Med 1978;126(4):343-61.
9. Al-Damluji SF, Al-Omari MM, Al-Fakhri S. Pulmonary alveolar microlithiasis in two siblings from Iraq. Br J Dis Chest 1973;67(3):246.
10. Hinshaw HC. Diseases of the chest. Philadelphia: WB Saunders, 1980:862.
11. Saputo V, Zocchi M, Mancosu M, et al. Pulmonary alveolar microlithiasis: a case report with a discussion of differential diagnosis. Helv Paediatr Acta 1979;34(3):245-55.
12. Caffrey PR, Altman RS. Pulmonary alveolar microlithiasis occurring in premature twins. J Pediatr 1965;66:758-63.
13. Sosman MC, Dodd GD, Jones WD, Pillmore GV. The familial occurrence of pulmonary alveolar microlithiasis. Am J Roentgenol Rad Ther Nucl Med 1957;77:947.
14. Crofton J, Douglas A. Respiratory diseases. Oxford: Blackwell Scientific Publications, 1975:686.
15. Fishman AP. Pulmonary diseases and disorders. New York: McGraw-Hill, 1980;965-87.

ENDOSCOPIC DIAGNOSIS AND EXTRACTION OF BILIARY ASCARIS: A CASE REPORT

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Infestation with the round worm *Ascaris lumbricoides* is one of the most common human helminthic diseases, occurring usually in developing countries in which hygiene is lacking.[1] The adult worm normally inhabits the small intestine. Migration and invasion into the biliary tree may cause biliary colic, recurrent pyogenic cholangitis, cholecystitis, and pancreatitis. There may be formation of biliary calculi that contain ova and fragments of adult worms.[2] In Saudi Arabia, ascariasis is uncommon.[3]

Case Report

A 53-year-old Syrian man was admitted to the hospital with a 7-day history of severe upper right abdominal pain and vomiting. Four years earlier he had had coronary artery bypass surgery, and at that time ultrasound diagnosis of silent gallstones was made. No previous history of recurrent jaundice or pain in the abdomen were elicited.

Liver function studies revealed bilirubin, 60 μmol/L (normal, 2 to 22 μmol/L); alkaline phosphatase, 183 U/L (normal, 36 to 125 U/L); aspartate transaminase, 66 U/L (normal, 11 to 55 U/L); and lactate dehydrogenase, 264 U/L (normal, 110 to 240 U/L). Results of other biochemical and hematologic tests were normal. Stool examination was negative for ova and parasites.

Ultrasound examination showed a dilated common bile duct and gallstones. Surgery was deferred in view of his previous cardiac surgery, and elective endoscopic retrograde cholangiopancreatography (ERCP) was performed 2 days after his admission to the hospital when longitudinal filling defect involving most of the common bile duct was noted. Endoscopic papillotomy was performed, and nasobiliary drain was inserted to decompress the dilated common bile duct. Repeat ERCP was performed 2 days later, and enlargement of papillotomy to 1 cm was performed. Dormia basket was inserted (Figure 1), and the end of the worm was gripped and slowly extracted through the endoscopic papillotomy (Figure 2) and finally retrieved by tripod forceps (Figure 3). No other ascaris worms were seen in the stomach or duodenum, and no other retained stones were obvious at this time. The patient experienced relief from his symptoms. He was treated with antihelminthic drugs and discharged home.

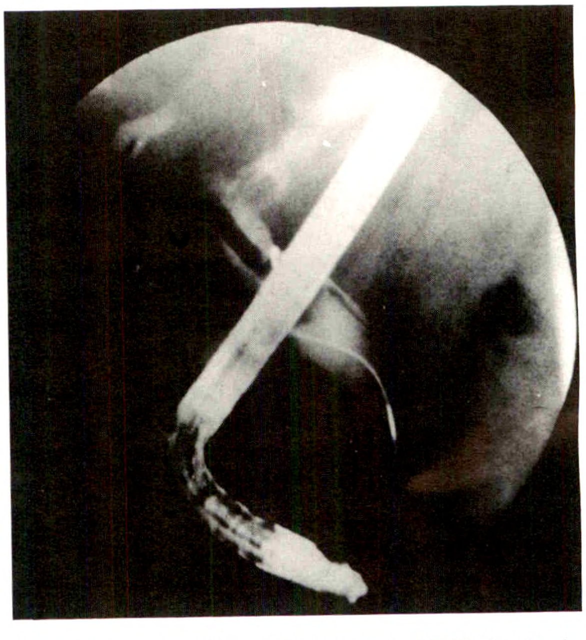

FIGURE 1. Ascaris as linear filling defect at ERCP showing in common duct with Dormia basket about to extract the worm.

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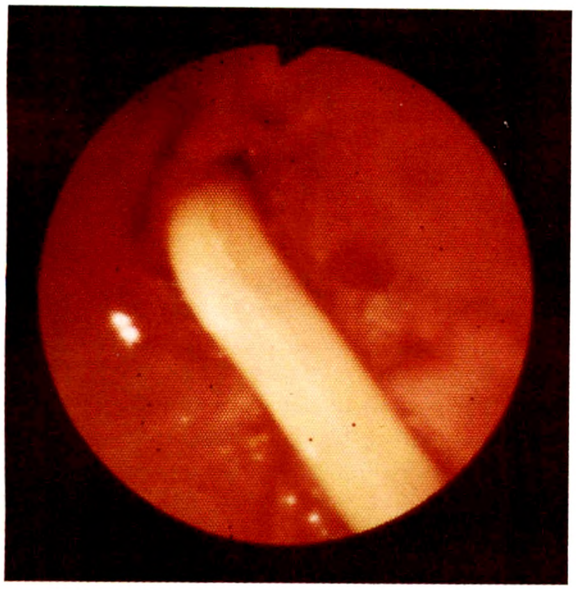

FIGURE 2. Endoscopic view of emerging ascaris through the papilla.

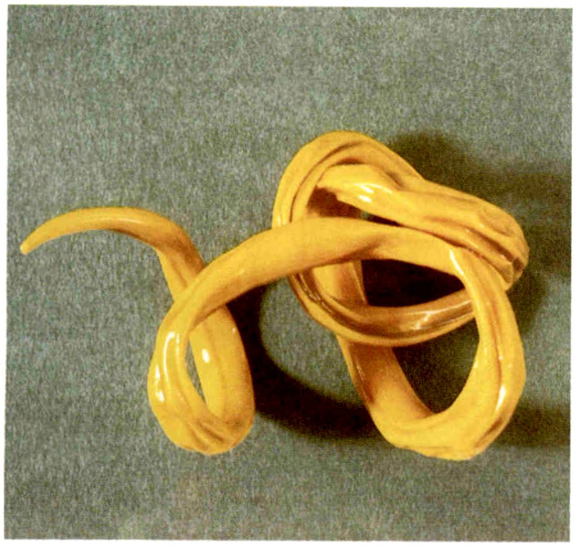

FIGURE 3. Ascaris after extraction through ERCP and sphincterotomy.

A repeat ERCP 1 month later to look for more worms or retained stones showed some retained stones in the common bile duct, which were extracted.

Discussion

Biliary ascariasis can be diagnosed by ultrasound of the abdomen[4] and contrast agent enhanced cholangiograph,[5] and recently it has been shown that ERCP[2] is an excellent diagnostic tool for demonstrating worms in the dilated common bile duct or intrahepatic duct. On the other hand, worms can mimic stones, as in this case.[6]

In this patient, formation of stones in the gallbladder and common bile duct may be secondary to ascaris, as the patient may have had ascaris infection prior to the initial ultrasound showing gallstones 4 years ago. There is supportive evidence that ascaris is the cause for biliary stones, and the stones related to ascaris are thought to form in the hepatic ducts and not the gallbladder.[2] Biliary lithiasis has also been reported with *Fasciola hepatica* and *Clonorchis sinensis*.[7]

Intestinal ascaris can be treated effectively with short courses of antihelminthics, but drug treatment has no effect on the worms inside the biliary ducts.[1,2] Instillation of piperazine citrate through a nasobiliary drain was used successfully.[8]

Previously, surgical treatment has been necessary for biliary ascariasis,[2,9] but recently a few reports have shown extraction of an ascaris worm from the biliary tree by Dormia basket through the papillotomy opening.[10,11]

References

1. World Health Organization Scientific Group. Control of ascariasis. WHO Tech Rep Ser 1967;379:1-39.
2. Khuroo MS, Zargar SA. Biliary ascariasis: a common cause of biliary and pancreatic disease in an endemic area. Gastroenterology 1985;88(2):418-23.
3. Abu Al-Saud AS. A survey of the pattern of parasitic infestation in Saudi Arabia. Saudi Med J 1983;4(2):117-22.
4. Schulman A, Loxton AJ, Heydenrych JJ, Abdulrahman KE. Sonographic diagnosis of biliary ascariasis. Am J Roentgenol 1982;139(3):485-9.
5. Cremin BJ. Biliary parasites. Br J Radiol 1969;42:506-8.
6. Schulman A. Non-western patterns of biliary stones and the role of ascariasis. Radiology 1987;162(2):425-30.
7. Yellin AE, Donovan AJ. Biliary lithiasis and helminthiasis. Am J Surg 1981; 142(1):128-36.
8. Kamath PS, Joseph DC, Chandran R, et al. Biliary ascariasis: ultrasonography, endoscopic retrograde cholangiopancreatography and biliary drainage. Gastroenterology 1986;91(3):730-2.
9. Turley K, Sherman RT. Biliary ascariasis. Am J Surg 1976;42(3):116-9.
10. Jessen K, Al-Mofleh I, Al-Mofarreh M. Endoscopic treatment of ascariasis causing acute obstructive cholangitis. Hepatogastroenterology 1986;33(6):275-7.
11. Manialawi MS, Khattar NY, Helmy MM, Burcharth F. Endoscopic diagnosis and extraction of biliary ascaris. Endoscopy 1986;18(5):204-5.

Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

Toxic Shock Syndrome and Staphylococcal Pneumonia in a Yemeni Patient

To The Editor: Staphylococcal toxic shock syndrome (TSS) is most commonly seen in menstruating women, although it has been reported after staphylococcal infection,[1] unrelated to the use of tampons or to menstruation.

Wilkins and colleagues[2] reported a case of partial TSS with staphylococcal pneumonia. Marchant and Brown[3] described a case of full TSS in staphylococcal pneumonia. I describe here a case of full TSS associated with staphylococcal pneumonia in a Yemeni patient.

A 19-year-old Yemeni man presented with fever, confusion, and hypotension. He gave a history of influenza-like illness about 2 weeks previously with sneezing, headache, vomiting, and mild cough. Three days prior to admission, he had diarrhea, vomiting, and cough productive of yellow sputum. He also had right lateral chest pain which increased with inspirations. He was admitted from the emergency room 48 hours later after a sudden deterioration in his mental state as observed by his parents.

On examination, he was very confused, tachypneic, and dehydrated. Central and peripheral cyanosis was detected, and body temperature was 40°C. Pulse rate was 160 beats per minute, with supine blood pressure of 70/50 mm Hg. There was dullness to percussion at the right lung base, reduced breath sounds, and a pleural rub. Chest x-ray film showed signs of right-sided pneumonia. Initial management was to combat shock in addition to administration of flucloxacillin and gentamicin after blood was taken for culture.

On the following day, he was more confused and had moderate neck stiffness; on this basis, a lumbar puncture was done, which revealed normal cerebrospinal fluid.

Two days later, he developed hyperemia of the conjunctiva and generalized erythema. Investigations showed white cell count of 18.5×10^9/L (reference range, 4.0 to 10.0×10^9/L) with heavy toxic granulation. Urinalysis revealed proteinuria and an excess of epithelial cells and large amounts of bile and blood. Malarial smear was negative as well as brucella agglutination and Widal test. Urine culture was sterile. Blood cultures were positive for *Staphylococcus aureus*; blood urea was 26.2 mmol/L, calcium 2.03 mmol/L, alkaline phosphatase 384 IU/L, and aspartate aminotransferase 55 IU/L. Ten days later he developed desquamation of the skin over the palms and soles.

When the diagnostic criteria for TSS were fulfilled, fusidate sodium was added to the antibiotics given before in addition to general supportive measures to combat shock. After 4 weeks, the patient's general condition started to improve, and he was discharged after 5 weeks.

This case fulfills the criteria for TSS[4] with fever, hypotension, desquamation, hyperemia of the conjunctiva, and evidence of multisystem involvement (vomiting, diarrhea, alteration in consciousness, impaired renal function, and decreased serum calcium). Although blood cultures were positive for *S. aureus* in this case, its isolation is not necessary for the diagnosis although most cases do have an identifiable source of infection.

The treatment of TSS must be directed primarily at the correction of shock and peripheral circulatory failure. Until results of cultures are available, antibiotic treatment must be broad spectrum. Although antimicrobial agents do not necessarily affect the outcome of the acute illness, they are recommended and have been given to most patients to eradicate the focus of toxin-producing staphylococcal bacteremia or bacteriuria and reduce the recurrence rate.[5] Sequelae of toxic shock syndrome have included reversible loss of hair and nails, prolonged weakness and fatigue, late onset rash, vocal cord paralysis, upper extremity paresthesis, protracted myalgia, disease recurrence, gangrene, amenorrhea, arthralgia, and coronary aneurysm.

The toxic shock syndrome has emerged as multifactorial staphylococcal disease and should be considered in all patients with appropriate signs and symptoms regardless of the patient's sex or menstrual state.

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References

1. Reingold I, Hargrett NT, Dan BB, et al. Nonmenstrual toxic shock syndrome: a review of 130 cases. Ann Intern Med 1982;96:871-4.
2. Wilkins EGI, Nye F, Roberts C, de Saxe M. Probable toxic shock syndrome with primary staphylococcal pneumonia. J Infect Dis 1985;11:231-2.
3. Marchant B, Brown J. Toxic shock syndrome and staphylococcal pneumonia. Lancet 1987;2(8558):578.
4. Shands KN, Schmid GP, Dan BB, et al. Toxic-shock syndrome in menstruating women: association with tampon use and Staphylococcus aureus and clinical features in 52 cases. N Engl J Med 1980;303(25):1436-42.
5. Chesney PJ, Crass BA, Polyak MB, et al. Toxic shock syndrome: management and long-term sequelae. Ann Intern Med 1982;96(pt 2):847-51.

High-Dose Iodine 131 Treatment of Hyperthyroidism

To the Editor: I read with interest the article by Dr. Johansen and his associates,[1] and I think some points related to high-dose iodine 131 treatment of hyperthyroidism deserve comment.

In this article, the authors did not mention the distribution of the patients in different categories of hyperthyroidism. Such factors as sex difference, age distribution, and severity of the disease ultimately have a significant effect on the response to treatment. It is obvious from the article that the majority of the patients did not have Graves' disease, but only 40% showed diffuse uptake in thyroid scan, which the authors also mentioned in the article. So the finding of small, firm, granular or nodular glands and palpations is not surprising, because the rest of the patients constitute a combination of toxic multinodular goiter, toxic adenoma, or Hashimoto's thyroiditis, which were documented by patchy uptake in thyroid scan. The incidence of 80% of the glands which are diffusely enlarged in hyperthyroidism, as documented in the Western literature, are of Graves' variety, whereas these patients include all varieties of hyperthyroidism, and so the percentage will be less. It is even documented that 20% of elderly patients with thyrotoxicosis may have firm, irregular, and not distinctly enlarged glands.[2]

Other clinical findings, such as ophthalmopathy, dermopathy, or severity of thyrotoxicosis, which help categorize different causes of hyperthyroidism, were not mentioned. Patients had high antimicrosomal and antithyroglobulin antibody titer, and so one can assume that at least a few patients could have Hashimoto's thyroiditis with transient thyrotoxic phase. The relevance of this fact is that they usually do not require treatment, least of all radioactive iodine therapy. The authors did not mention whether antithyroid drugs were given before submitting the patients for radioactive iodine treatment or not, and if at all given, how long the patients took the medicines to become euthyroid. It is necessary to administer antithyroid drugs before giving radioactive iodine treatment in patients who are having severe thyrotoxicosis or thyrocardiac disease to achieve a eumetabolic state to avoid thyrotoxic crisis.

Though this mode of treatment is advantageous where follow-up is difficult, one should be particular about the severity and variety of thyrotoxicosis before instituting this kind of treatment to prevent avoidable complications.

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References

1. Johansen K, Khan M, Woodhouse NJY. High-dose

iodine 131 treatment of hyperthyroidism: experience at King Faisal Specialist Hospital and Research Centre. Ann Saudi Med 1988;8(6):466-9.
2. Wilson JD, Foster DW, eds. Williams textbook of endocrinology, 7th ed. Philadelphia: WB Saunders, 1985:755.

The letter was referred to the authors of the article in question who offer the following reply:

Dr. Bandyopadhyay's letter reiterates several points already made in the article, the purpose of which was to discuss high-dose radioactive iodine 131 (^{131}I) therapy and not to list the already well-documented clinical features of thyrotoxicosis. Hashitoxicosis in our opinion should be treated with therapeutic ^{131}I, particularly in view of the follow-up difficulties discussed in the paper.

All the patients were treated with beta-blockers before and for 1 month after ^{131}I administration. A few patients with severe disease were also controlled with antithyroid drugs as well before the therapy dose was given.

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Altered Organization of Antenatal Care in a Rural District

To the Editor: During 1986 the antenatal care in the Al-Majma'ah Region was reorganized,[1] and we wish to describe some interesting results of this reorganization.

During 1987 no maternal deaths occurred. Some obstetric data are shown in Table 1. The perinatal mortality rate declined from 4.7% in 1986 to 2.5% in 1987. The stillbirth rate was 1.0% in 1987 as compared to 2.2% in 1986; the probable causes of stillbirth are shown in Table 2. The total number of visible major malformations was five cases in 1987 (three were among the stillbirths). The reduction in the stillbirth rate was pronounced among Saudi women (21 stillbirths in 1986 versus nine in 1987), whereas no change was observed in the non-Saudi group. Only two cases of abruptio placentae were seen in 1987. The number of cord complications was unchanged. As in 1986 there was only one case of intrauterine fetal death due to preeclampsia. One case of intrauterine fetal death was caused by infection in 1987. The patient had premature contractions in the 28th week of gestation. She refused admission although there was a history of premature rupture of the membranes. A few days later she came to the hospital with breech presentation and refused operative delivery. The baby died before the delivery. Its birth weight was 1700 g, and histopathologic examination of the placenta showed acute inflammatory changes of the membranes.

In this follow-up study the WHO classifications and definitions[2] were used so the data were com-

TABLE 1. *Some obstetric data.*

	1986 No. (%)	1987 No. (%)
Total no. of deliveries (>500 g)	987	1102
Saudi	815(83)	893(81)
Non-Saudi	172(17)	209(19)
Twin deliveries	10(1)	5(0.5)
Total no. of newborns	997	1107
Primipara	154(16)	186(17)
Multipara (2-6 deliveries)	632(64)	650(59)
Grand multipara (> 7 deliveries)	201(20)	266(24)
Infants with birthweight <2500 g	88(9)	84(8)
Cesarean sections	74(7.5)	61(5.5)
Emergency	65	47
Elective	9	14

TABLE 2. *Probable causes of stillbirths.*

	No. in 1986	No. in 1987
Abruptio placentae	5	2
Cord complications	4	3
Undetected diabetes mellitus	3	0
Infection	1	1
Preeclampsia	1	1
Malformations	3	1
Road traffic accidents	0	1
Unknown	5	2
Total	22	11

parable to those reported by Thomassen et al.[1] In 1986 Thomassen found a perinatal mortality rate of 4.7%, while a rate of 3% to 4% was thought to be representative for the Kingdom as a whole in 1985.[3]

From December 1986, a systematic training program started for all the doctors and midwives in our region. From the beginning of 1987 we established antenatal clinics in 11 primary health care centers. The percentage of "unbooked" patients declined from 33% in 1986 to 17% in 1987, and more than 80% of the Saudi women and 90% of the non-Saudi women who delivered at our hospital had been to one or more antenatal check-ups in 1987. The number of obstetric ultrasound examinations rose from 1549 in 1986 to 2874 in 1987, and several midwives are now trained to do the screening procedure.

As already pointed out by Thomassen et al,[1] brucellosis is the most common infection during pregnancy in our region. In 1987, 55 patients with brucellosis were treated, of whom six aborted during the first trimester. There were no stillbirths due to untreated brucellosis.

In December 1986, screening for diabetes mellitus in pregnancy was established. In 1987, 37 cases of diabetes were treated compared with five cases in 1986. Since the start of the screening program there has been no case of undetected diabetes in the group of intrauterine fetal deaths, and no perinatal mortality among those treated for diabetes.

We believe that a well-organized antenatal organization including screening for diabetes mellitus and brucellosis and under supervision of obstetricians and skilled midwives is the most effective and least expensive tool in the struggle for lowering the stillbirth rate and perinatal mortality in rural districts of Saudi Arabia.

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References

1. Thomassen PA, Langemark L, Kumar R. Stillbirths and antenatal care at a general hospital. Ann Saudi Med 1989;9(2):186-9.
2. Chiswick ML. Commentary on current World Health Organization definitions used in perinatal statistics. Br J Obstet Gynaecol 1986;93:1236-8.
3. Ohlsson A. Better perinatal care in Saudi Arabia. Ann Saudi Med 1985;5(3):169-78.

Chest Wall Hamartoma in an Adult

To the Editor: A hamartoma is not a true neoplasm but a disorganized overgrowth of normal tissues attributed to an error in development. It is present at birth or appears soon afterward. It grows with the patient and ceases to grow when general body growth ceases. This lesion occurs in many tissues and frequently in the lung. It has occurred only rarely in the chest wall, and then in children under 1 year of age.

A 44-year-old woman presented to a peripheral hospital with pain and tenderness in the posterior aspect of the lower chest. A chest x-ray film showed a pleural mass in the left side of the chest posterolaterally. There was no evidence of rib erosion (Figure 1). An open biopsy was performed on the lesion, and histologic examination suggested that it was a mesothelioma. The patient was transferred to King Faisal Specialist Hospital,

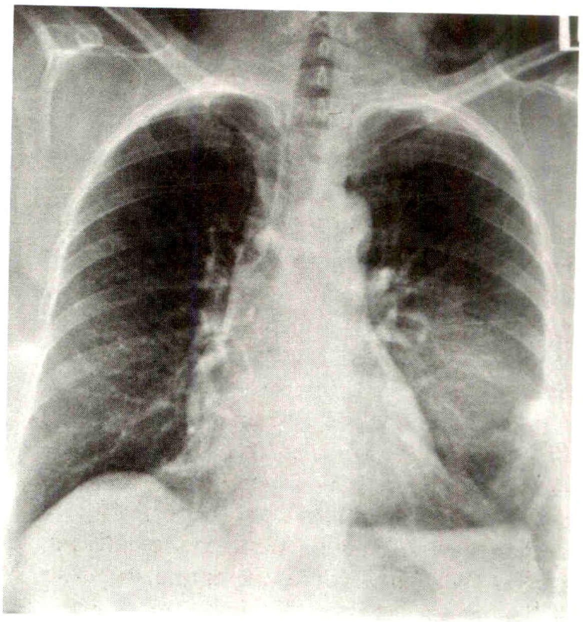

FIGURE 1. Chest roentgenogram shows pleural mass in the left side of the chest with no evidence of rib erosion.

where a thoracotomy was performed to widely excise this lesion. Frozen section performed peroperatively showed no evidence of malignancy, and the tumor was avulsed quite easily from the chest wall. It had not invaded the ribs. Permanent histopathologic sections showed a mixture of cartilaginous, fibroadipose, and muscular tissue. The cartilage consisted of mature chondrocytes, and in some areas benign mesothelial cells were seen (Figure 2). The patient made an uneventful postoperative recovery.

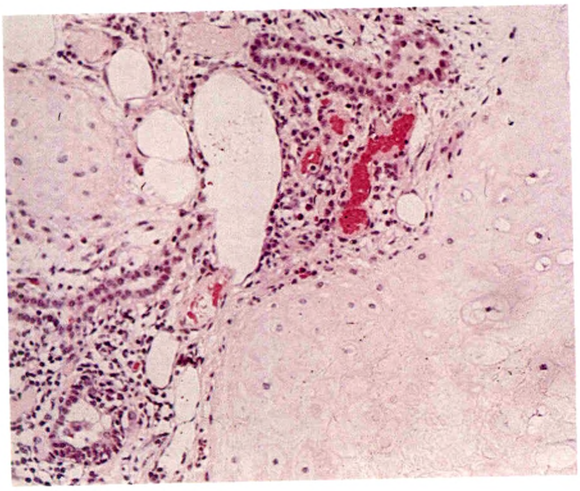

FIGURE 2. Photomicrograph showing mixture of benign adipose tissue, cartilage and spaces lined by mesothelial cells (hematoxylin and eosin stain, original magnification, ×40).

Following a literature search we found no other report of this lesion occurring in the chest wall of an adult. It is likely that this lesion was present for many years, probably since birth, but there was no record of any previous chest x-ray examination of this woman. The onset of symptoms precipitated excision.

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Familial Mediterranean Fever

To the Editor: I read with great interest the letter by Dr. Fahim.[1] He mentioned that "no patients have been reported from the Arabian peninsula." I would like to describe my experience with a patient with familial Mediterranean fever whom I have been treating for 2 years.

A 20-year-old unmarried Saudi woman was admitted to the hospital with complaints of pain in the left hypochondrium, anorexia, and frequent vomiting for the past 6 hours. There was no history of sore throat, cough, loose motions, urinary difficulty, or joint symptoms. She had not gone abroad in the last 2 years, and there was no family history of similar complaints.

Examination revealed a thin girl with temperature of 38°C; her pulse was 100 beats per minute and blood pressure was 110/70 mm Hg. Her throat appeared normal, and there was no lymphadenopathy. There was tenderness with rigidity in the epigastrium and left hypochondrium, and bowel sounds were diminished. Other physical findings were normal.

Her hemoglobin was 12.1 g/L; leukocyte count, $19.6 \times 10^9/L$ with differential fractions of 0.82 polymorphonuclear leukocytes and 0.18 lymphocytes. The erythrocyte sedimentation rate (ESR) was 103 mm/h; results of urinalysis were normal. Results of liver function tests, Widal and brucella agglutination tests, and blood culture were normal. Antinuclear factor and rheumatoid factor were negative. Abdominal ultrasound and plain roentgenogram, as well as endoscopy of the upper gastrointestinal tract were normal.

As there were no definite diagnostic criteria for diagnosis of familial Mediterranean fever, in this case diagnosis was eventually made by excluding possible causes and by combination of recurrent attacks of localized peritonitis with polymorphonuclear leukocytosis and elevated ESR. This patient has been admitted six times during the past year, and her symptoms, signs, and investigation results were similar on each occasion. During each admission she presented with symptoms of pain in the upper abdomen, vomiting, and fever, and her symptoms subsided with symptomatic treatment in 7 to 10 days.

After the diagnosis of familial Mediterranean fever was established, she was treated with colchicine in gradually reducing doses, and her symptoms subsided within 3 to 7 days.

The patient was advised to take colchicine, 1 mg daily for prophylaxis, but she could not tolerate it on a continuous basis. Now she is given colchicine at the first onset of symptoms (similar to this drug's use in the treatment of gout).

The report of this case should alert treating physicians about the possibility of this diagnosis when a patient has recurrent attacks of low-grade fever, gastrointestinal symptoms, localized peritonitis, polymorphonuclear leukocytosis, raised ESR, and absence of other positive findings.

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Reference

1. Fahim AS. Familial Mediterranean fever in Yemen Arab Republic. Ann Saudi Med 1988;8(6):512-3.

CURRENT CONCEPTS IN PATHOLOGY AND LABORATORY MEDICINE SYMPOSIUM
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GLOMERULONEPHRITIS IN SAUDI ARABIA, M Akhtar, King Faisal Specialist Hospital and Research Centre, Riyadh

A series of 497 renal biopsies seen at our laboratories between July 1983 to August 1988 were reviewed. Patients ranged in age from 3 months to 72 years. A total of 107 biopsy specimens were from renal allografts, while 380 were from native kidneys. Of the 107 transplant biopsies, 97 showed rejection, four had acute tubular necrosis, two had cyclosporin toxicity, and four showed glomerulonephritis. In the specimens from native kidneys, the diagnoses were minimal change disease in 16 (4.2%); mesangioproliferative glomerulonephritis, 80 (21.0%); focal segmental glomerulosclerosis, 96 (25.2%); membranoproliferative glomerulonephritis, 29 (7.6%); membranous glomerulonephritis, 18 (4.7%); rapidly progressive glomerulonephritis, 12 (3.1%); IgA nephropathy, 16 (4.2%); postinfectious glomerulonephritis, 8 (2.1%); lupus nephritis, 36 (9.4%); other systemic diseases, 40 (10.5%); and miscellaneous conditions, 29 (7.6%). This review revealed an unusually high incidence of focal and segmental glomerulosclerosis and mesangioproliferative glomerulonephritis and a low incidence of IgA nephropathy. There was no case of type II membranoproliferative glomerulonephritis (dense deposit disease).

NEW DEVELOPMENTS IN METHODOLOGY, ES Baginski, King Faisal Specialist Hospital and Research Centre, Riyadh

The development of methodology in clinical chemistry has exploded in recent years both in refinement and scope. The emphasis has been on the determination of hormones, drugs, and their metabolites, using immunoassays aided by sophisticated instrumentation. Once known only as research tools, instruments such as gas and liquid chromatograph, mass spectrometer, and atomic absorption spectrophotometer are now used routinely in many clinical laboratories. There is a growing demand to provide test results faster and perform assays more accurately to aid in the diagnosis, prognosis, and treatment of the ever-growing world population. Environmental contaminants affecting health add further to the growing list of compounds to be analyzed. Therapeutic drugs and antibiotics are now routinely monitored in blood, owing to the development of simple immunoassays based on monoclonal antibodies specific for either intact compounds or their metabolites. One of the new trends in dealing with identification of congenital diseases is by DNA probing at a very early stage in life. There is a resurgence in the use of electrophoresis. Highly refined techniques have been developed, including two-dimensional electrophoresis aided by computer mapping of the bands. Capillary electrophoresis shows promise in the separation of microquantities of compounds including DNA fragments. The trend seems to continue in the direction of refinement of methods and more sophisticated instrumentation aided by computers.

FINE-NEEDLE ASPIRATION BIOPSY: KFSH&RC EXPERIENCE, MA Ali, King Faisal Specialist Hospital and Research Centre, Riyadh

In recent years, the fine-needle aspiration biopsy procedure has attained worldwide recognition and is used increasingly. At the King Faisal Specialist Hospital and Research Centre, a total of 5505 fine-needle aspiration biopsies were performed between 1976 and 1987. Of these biopsies, 4755 (86%) were done in adults and 750 (14%) were performed in children. A total of 1651 biopsies (30%) were performed on lesions of the head and neck excluding thyroid. Thyroid biopsies numbered 432 (8%); breast, 529 (9.5%); lung plurae/mediastinum and chest, 513 (9%); abdomen and pelvic organs excluding liver, 648 (12%); liver, 409 (7.5%); extremities, 647 (12%); testes and prostate, 282 (5%); and other miscellaneous sites, 394 (7%). In 2584 cases (47%), diagnosis of malignant disease was established based on fine-needle aspiration biopsy. In 2418 cases (44%), a diagnosis of a benign disease or normal tissue was rendered. In 503 cases (9%), the fine-needle aspiration biopsy was considered nondiagnostic, inconclusive, or unsatisfactory.

INCIDENCE AND SIGNIFICANCE OF *CAMPYLOBACTER PYLORI* IN GASTRIC BIOPSIES IN SAUDIS, JE Beecham, H Khan, Y Shoubaki, L Hawa, King Fahad National Guard Hospital, Riyadh

Chronic gastritis is a worldwide disease affecting from 20% to 50% of the adult population. A recent study in Saudis attending an endoscopy clinic found histologically proved chronic gastritis in 74%. Evidence suggesting chronic gastritis, however, has long been felt to be unsatisfactory since gastritis symptoms frequently recur or persist despite therapy. Recently, it has been suggested that *Campylobacter pylori*, initially found by the Australian research team of Warren and Marshall, growing in the mucous layer of the gastric antrum might be causative in the disease and that antibiotic therapy may play a role in the control of chronic gastritis. However, the organism is also found in 5% to 15% of normal individuals. To assess the incidence and significance of *C. pylori* in Saudis, 95 gastric biopsy specimens taken from 88 Saudi patients attending the King Fahad Hospital Endoscopy Clinic were examined for evidence of *C. pylori* by light microscopy and culture. Histologic evidence of chronic gastritis was found in 95% of individuals, though it was suspected endoscopically in only 55%.

C. pylori was demonstrated in 77 of 88 patients (88%) by histology or less sensitively by culture. The histologic presence of chronic gastritis correlated statistically with the presence of *C. pylori* ($P < 0.001$). The organism was found in one of four patients (25%) not demonstrating histologic chronic gastritis. This very high incidence of *C. pylori* and histologically proved chronic gastritis did not correlate with symptoms of gastritis or endoscopic suspicion of gastritis, thus limiting clinical usefulness.

A BLOOD BANK METHOD FOR PRODUCING HIGH-PURITY, HIGH-YIELD F VIII CONCENTRATE FOR TREATMENT OF HEMOPHILIC PATIENTS, S Bernvil, J Schifano, K Wallevik, King Faisal Specialist Hospital and Research Centre, Riyadh

The need for F VIII concentrates to treat hemophilia A patients is constantly rising due to the fact that more patients are being identified and treated and more intensive treatment programs are being adopted worldwide to protect patients from long-term sequelae of hemorrhages. The need for donor plasma is rising more steeply as a consequence of technological advances allowing for high purification of F VIII concentrates, unfortunately leading to substantial loss of F VIII during the purification process. The routine use of virucidal techniques has further decreased the yield to create a worldwide shortage of F VIII. In view of this, it is mandatory that each country establishes a national plasma fractionation service so that every blood donation contributes to the pool of fresh-frozen plasma. A method has been developed to extract F VIII from heparinized fresh-frozen donor plasma, using equipment available in most large blood banks. The product lends itself to lyophilization and heat treatment at 68°C for 24 hours and has a final specific activity (F VIII units/mg protein) of 2 or better, with low levels of fibrinogen (4 g/L) and an overall yield of 40% to 45% of the raw material. The F VIII recovery is more than twice the average yield for comparable commercial products. The in vivo recovery and biological half-life is fully within expected limits for F VIII concentrates. The red cells are recovered for clinical use by resuspension in CPDA after centrifugation of the heparinized blood and removal of plasma. The fractionation method is currently being implemented at KFSH&RC.

MOLECULAR BIOLOGY OF THE t(14;18) CHROMOSOMAL TRANSLOCATION IN NON-HODGKIN'S LYMPHOMA: IMPLICATIONS FOR DIAGNOSTIC PATHOLOGY, ML Cleary, Stanford University Medical Center, Stanford, California

Recent studies on the molecular biology of t(14;18) translocations in non-Hodgkin's lymphomas illustrate how fundamental observations of chromosomal aberrations in human cancer can result in remarkably novel strategies for diagnosing and detecting specific neoplasms. The t(14;18) karyotypic abnormality is associated with almost all lymphomas showing a follicular morphology, and molecular studies have demonstrated that t(14;18) results in the juxtaposition of a gene on chromosome 18, termed *bcl*-2, with the IgH gene on chromosome 14. The *bcl*-2 gene has been structurally characterized and shown to encode a previously undescribed protein that is presumably involved in the pathogenesis of t(14;18) carrying lymphomas. Since t(14;18) translocation breakpoints tend to cluster at discrete sites within or flanking the *bcl*-2 gene, chromosomal probes from near the breakpoints can be used to detect translocations on Southern blots in much the same way as antigen receptor rearrangements. This has permitted so-called molecular cytogenetic analyses for the prevalence of *bcl*-2 alterations in a wide variety of hematolymphoid neoplasms and prompted early studies of their prognostic significance. Additionally, oligonucleotide primers flanking breakpoint cluster regions can be used to specifically amplify DNA containing the translocation breakpoint by a procedure known as the polymerase chain reaction. One out of a million t(14;18) lymphoma cells can be detected by this method which represents an important advance in lymphoma diagnosis and staging. Antibodies directed against the *bcl*-2 protein have been used to show that overexpression of the *bcl*-2 protein is a specific marker for t(14;18) lymphomas, and its immunological detection may be very helpful in distinguishing benign from neoplastic follicular lymph node lesions.

APPLICATIONS OF IMMUNOGLOBULIN AND T-CELL RECEPTOR GENE REARRANGEMENTS IN DIAGNOSTIC PATHOLOGY, ML Cleary, Stanford University Medical Center, Stanford, California

Detectable gene rearrangements secondary to somatic DNA alterations serve as useful markers for the diagnosis and characterization of a growing number of neoplasms. Rearrangements of immunoglobulin (Ig) and T-cell receptor (TCR) genes have proved to be very useful lineage and clonal markers for lymphoid malignancies since the capacity to rearrange these antigen receptor genes is limited to hemopoietic tissues. Their usefulness is also based on the unique molecular anatomy of the genes and the physiologic steps required for their expression which represent very early events in B- and T-cell ontogeny. Analysis of rearranged Ig genes has provided objective evidence for lineage derivation in leukemias and lymphomas which otherwise have not expressed Ig protein, the conventional marker for establishing B lineage and clonality, and TCR rearrangements are the only available clonal markers for T-cells. Most cases of non-B, non-T "null cell" lymphomas lacking definitive phenotypic markers of B or T differentiation contain rearranged Ig genes, an important characteristic indicating B-cell derivation. Rearranged Ig or TCR genes have also indicated a B-cell derivation for "hairy cell leukemia" and a potential T lineage for so-called "true histiocytic" neoplasms. Several studies have looked at gene rearrangements in Hodgkin's disease with conflicting results probably because of the heterogeneous cellular composition and the scarcity of Reed-Sternberg cells in the tissues. Diagnostically, gene rearrangements can be an accurate and sensitive indicator of clonal lymphocyte proliferation, although it is now clear that they may not be markers for malignant clinical behavior since clinically benign diseases such as Sjogren's syndrome and lymphomatoid papulosis contain clonal populations of B or T cells, respectively, as determined by gene rearrangement analyses.

CURRENT CALCIUM PROBLEMS, AM Bold, King Faisal Specialist Hospital and Research Centre, Riyadh

The routine assays for parathyroid hormone (PTH) do not directly measure biologically active PTH, and all have limitations. The recently introduced two-site intact molecule assay for PTH has theoretical advantages. First-generation ionized calcium analyzers are simple to operate, and precise results can be obtained within 60 seconds. With these, the laboratory can measure the biologically active calcium fraction routinely, especially in situations where the level of total calcium is clinically misleading. In the United States alone, the cost of treatment for hip fractures due to osteoporosis costs several billion dollars annually and is rising steeply. A laboratory requirement is a simple, reliable, and quantitative bone marker to help in early diagnosis of osteoporosis and for monitoring response to treatment. Old favorites such as alkaline phosphatase and urine hydroxyproline have been joined by new tests such as osteocalcin and galactosyl hydroxyproline.

APPLICATION OF DNA PROBES IN CLINICAL MICROBIOLOGY, F Al-Dayel, King Faisal Specialist Hospital and Research Centre, Riyadh

The rapid progress in the technologies of nucleic acid hybridization and recombinant DNA methods has made it possible to use these techniques in diagnosis of different infectious diseases. Currently, there are many types of probes available for clinical diagnosis of bacterial infections such as *Mycobacterium* sp., *Mycoplasma* sp., *Legionella* sp., *Campylobacter* sp., and bacteria causing sexually transmitted diseases including chlamydia trachomatis. The use of probes has been extended to include many viral infections, e.g., CMV and HSV, and parasitic infections, e.g., leishmaniasis. DNA probes offer many important advantages such as rapid organism identification, screening specimens for a select group of organisms, and detection of nonviable organisms (which is important in cases of viral diseases). On the other hand, the disadvantages of DNA probes limit their uses in the clinical microbiology laboratory. Some of these disadvantages include the radiometric identification methods and the lack of expertise for interpreting results. The sensitivity and specificity of these different types of probes vary, being highly sensitive and specific for some organisms while less sensitive and specific than the other commercial tests for other organisms. In conclusion, DNA probes start to have a great impact on patient care, and they are under strong development to be one of the prominent areas in future microbial diagnosis.

DNA REPAIR DEFICIENCY AND ITS IMPLICATION FOR MALIGNANCY, MA Hannan, King Faisal Specialist Hospital and Research Centre, Riyadh

An association between DNA repair deficiency and cancer has been indicated in inherited disorders like ataxia-telangiectasia (AT) characterized by radiation sensitivity and predisposition to malignancies. A partial deficiency in DNA repair and an excess risk of cancer mortality have also been found in AT heterozygotes. The heterozygous carriers of genes for such disorders, prevalent in the population, are believed to represent a good percentage of the adult cancer victims. This hypothesis implies that many cancer patients would have an underlying defect in DNA repair. Experiments aimed at verifying this hypothesis not only have been limited but also have produced conflicting results warranting further studies. We have analyzed in vitro radiosensitivity of peripheral blood lymphocytes and of skin fibroblasts from a number of Saudi patients presenting with non-Hodgkin's lymphoma (NHL) and several apparently healthy members of a "cancer family." Our data, in contrast with results reported by others, demonstrate an increased radiosensitivity in cells from the majority of the NHL patients indicating an underlying abnormality of DNA repair. Similar results were also obtained in nearly half of the "cancer family" members, suggesting a segregation of the factor controlling radiosensitivity. These data were discussed with an emphasis on the usefulness of a cell survival assay after chronic irradiation in detecting radiosensitivity/DNA repair deficiency in cancer patients as well as "cancer prone" individuals.

IMMUNOPEROXIDASE IN SURGICAL PATHOLOGY: THE TRUTH, A Haleem, Riyadh Armed Forces Hospital

Immunoperoxidase is taking a bigger role in diagnostic surgical pathology. The purpose of this paper is to review the recent literature to find out the pros and cons of this technique and to present our own experience with it. In general, this technique is considered to be an extremely useful adjunct to histology. It is mainly used for the identification of undifferentiated tumors, but is more specific for different hormones, viruses, fungi, and parasites. The advent of monoclonal antibodies has improved the specificity of this technique. More and more reports, however, are coming up with ever-increasing lists of cross reactivities with these antisera. To avoid this, it is advised to apply a panel of antisera in order to correlate the negative and the positive results, which in turn are interpreted in the light of the morphologic appearances. In our experience, inactivity of the antisera is the biggest problem. When effective, the antisera against the EMA, CLA, and Ig give the best results on paraffin sections, with a positive contribution to the diagnosis in 76%, 71%, and 40% of the cases, respectively. In our series of undifferentiated tumors, 58% were diagnosed as lymphomas, 20% carcinomas, and 6% neuroblastomas. Immunoperoxidase was not helpful in the remaining 16% of the cases.

ROLE OF ONCOGENES IN HEMATOLOGIC MALIGNANCY, SS Hussain, MA Hannan, King Faisal Specialist Hospital and Research Centre, Riyadh

Oncogenes are derived from proto-oncogenes which discharge important regulatory functions in cell proliferation. They seem to act in concert in cells under conditions in which the inhibitory controls on growth have broken down. Some of the oncogenes known to participate in hematologic neoplasia are c-myc, c-mil, c-abl, N-ras, c-Ha-ras, T-lym and tx-1 to tx-4, representing a sampling of sequences coding for nuclear and cytoplasmic proteins with various locations and functions. Besides oncogenes, the genetic background contributing to the proneness to the malignant phenotype is provided by genes affecting metabolism of carcinogens, repair functions, and immunosurveillance. In this perspective, oncogenes form but one element in the cascade of events leading to malignancy. Nevertheless, on the one hand, they offer useful diagnostic tools on which prognostic evaluations could be based with confidence and, on the other, give important leads to the understanding of cell control mechanisms. In view of this premise, a project is just underway at our laboratory on the study of non-Hodgkin's lymphoma in Saudi Arabia. Within the framework of this project, analysis is being carried out for oncogene expression on the tissues of graded patients and patients classified as repair-proficient and repair-deficient.

PROGRESS IN HORMONE ASSAYS, BG Joyce, Riyadh Armed Forces Hospital

Methods for the quantitative determination of hormone levels in biological fluids and tissues have evolved at a considerable rate in the last 50 years, the greater part of this advancement being in the last two decades. The semiquantitative bioassays and relatively crude physiochemical methods such as spectrophotometry, gas-liquid chromatography (GLC), thin-layer chromatography (TLC), and competitive protein-binding (CPB) assays have been largely replaced by the more sophisticated immunoassays which were originally proposed by Yalow and Berson. Many of these early immunoassay procedures involved laborious and time-consuming sample preparation and purification before the end-point determination. Initially, these methods were crude and insensitive and achieved analytical specificity by incorporating various forms of chromatographic separation of the hormone being quantitated from structurally similar compounds present in the biological matrix. The introduction of monoclonal antibody technology into hormone immunoassays and the rapidly developing microchip industry have together produced a range of sophisticated instrumentation for measuring hormone concentrations in the picomolar to nanomolar range. With the advent of nonisotopic immunoassays laboratories can now provide a stable, robust, specific, sensitive, precise, and accurate procedure for the diagnosis and subsequent monitoring of treatment of a wide range of clinical syndromes.

ARTIFICIAL INTELLIGENCE IN A CLINICAL LABORATORY, LR Karstetter, King Faisal Specialist Hospital and Research Centre, Riyadh

The concept and applicability of the new development of artificial intelligence on computers in relation to the practice of laboratory medicine have been explored. With the increasing use of computers in the laboratory, it is natural that breakthroughs in computer technology will be incorporated into the practice of laboratory medicine. Such is the case with the current evolution of special hardware and software designed to transform computers from merely fast gatherers and regurgitators of information into "thinkers" which can analyze and solve problems, using information in much the same way as humans. A brief explanation of artificial intelligence and how it works was given with the current similarities and divergencies between what is now being termed silicon-based versus carbon-based intelligence. "Expert" systems developed, such as Caduceus and Mycin, have been examined. Finally, the implications of this technology are exciting and revolutionary to the future practice of laboratory medicine as we begin to watch the emergence of the "electronic colleague."

ULTRASTRUCTURAL CYTOCHEMISTRY AND IMMUNOELECTRON MICROSCOPY OF LEUKEMIC CELLS, SH Khalil, King Faisal Specialist Hospital and Research Centre, Riyadh

It is now possible to diagnose and classify most cases of acute leukemia using light microscopy and cytochemistry. However, about 5% to 10% of cases of acute leukemia remain unclassified using the above procedures and are consequently put into an acute undifferentiated leukemia group. Ultrastructural cytochemistry and immunoelectron microscopy have increased the potential for morphologic analysis of leukemic cells by electron microscopy (EM). The presence of myeloperoxidase in otherwise undifferentiated leukemic blasts is regarded as a sign of myeloid differentiation and an important criterion for diagnosis of acute myeloid leukemias. The different reactivity patterns of acid phosphatase, when viewed with the EM, may have diagnostic value. For example, the presence of small lysosomal granules with acid phosphatase activity is an early feature of monocytic differentiation. On the other hand, the presence of a strong focal acid phosphatase reaction in granules and Golgi membranes is a characteristic feature of leukemic T cells with an immature membrane phenotype. Of particular interest for ultrastructural studies has been the development of a technique whereby electron-dense colloidal gold particles of various sizes are coupled to antibodies of well-defined specificities, thus serving as marker molecules easily visualized under the EM. The combination of cytochemistry with immunogold staining in the same EM preparation has the advantages of both methods and permits the precise characterization of cells reactive with a particular monoclonal antibody.

CURRENT CONCEPTS OF BONE MARROW TRANSPLANTATION: KING FAISAL SPECIALIST HOSPITAL EXPERIENCE, MA Padmos, for the Bone Marrow Transplant Team, King Faisal Specialist Hospital and Research Centre, Riyadh

Allogeneic bone marrow transplantation has been performed at King Faisal Specialist Hospital and Research Centre since April 1984. In the first 4 years, a total of 100 patients received bone marrow transplants from HLA compatible, MLC nonreactive sibling donors. Patients were prepared with cyclophosphamide and total body irradiation or busulfan and cyclophosphamide or cyclophosphamide alone. Cyclosporin was used for prophylaxis of graft-versus-host disease in all but four patients. Among 48 patients with acute leukemia, 25 are alive, with 17% relapse/rejection rate and 52% survival. Twenty-two patients had chronic leukemia; 10 are alive, with 9% relapse/rejection and 46% survival. Twenty-two patients had aplasia; 12 are alive, with 18% relapse/rejection and 56% survival. Eight patients were categorized as "other"; five are alive, with 13% relapse/rejection and 63% survival. Overall, 52 of the total 100 patients are alive, with a 15% relapse/rejection rate and 52% survival. Newer methods are expected to improve morbidity and mortality results.

AUTOMATION AND MECHANIZATION IN CLINICAL MICROBIOLOGY, SMH Qadri, King Faisal Specialist Hospital and Research Centre, Riyadh

Unlike chemistry and hematology, clinical microbiology remains one of the most labor- and skill-intensive disciplines of laboratory medicine. Many of the procedures are manual; they are growth-dependent and require 36 to 48 hours, with few exceptions, before crucial information is available to the clinician for optimal patient care. Notable progress has been made during the last 15 to 20 years to mechanize and automate clinical microbiology. Instruments have been developed that can stain bacterial smears, prepare microbiological media in hands-off operations, pour the media in plates, streak clinical specimens on appropriate media, detect and identify microorganisms, and perform antimicrobial susceptibility testing. Today, automated identification of medically significant microorganisms and determination of their drug sensitiveness can be accomplished in 4 to 6 hours after their isolation. Although automation and mechanization in diagnostic microbiology are still in their infancy, significant advances have been made to acquire critical information for patient care more rapidly than manual procedures permit. The purpose of this presentation was to describe some of these developments and their clinical relevance to provide useful microbiological information for better patient care.

QUINOLONE ANTIMICROBIAL AGENTS AND *BRUCELLA MELITENSIS*, ERJ Pavillard, King Faisal Specialist Hospital and Research Centre, Riyadh

Quinolone carboxylic acid derivatives, which are structurally related to nalidixic acid, are the major advance in antimicrobial therapy in this decade. They are rapidly bactericidal due to inhibition of bacterial DNA gyrase which is responsible for supercoiling of DNA within the bacterial cell. Quinolones are not subject to infectious plasmid-mediated bacterial resistance. When resistance occurs, it is by way of chromosomal mutation, and therefore a less frequent event. The minimum inhibitory concentration of the quinolone-ciprofloxacin for the majority of *Brucella melitensis* isolates is 0.7 to 1.0 μg/mL, and the minimum bactericidal concentration is close to this range. *Brucella melitensis* is mainly an intracellular parasite, particularly of macrophages, and importantly, ciprofloxacin is concentrated in these cells. Theoretically, quinolone derivatives have considerable potential for treating brucellosis, and clinical trials are in progress to investigate this possibility.

CLONAL EVOLUTION IN CHRONIC MYELOID LEUKEMIA: IDENTIFICATION OF CELL TYPE IN BLAST CRISIS AND PREDICTION OF TYPE OF BLAST CRISIS IN CHRONIC PHASE, GT Roberts, MA Padmos, R Elmes, DG Spence, H Clink, P Ernst, King Faisal Specialist Hospital and Research Centre, Riyadh

Chronic myeloid leukemia (CML) is a neoplastic disorder of hematopoietic stem cells which runs a relatively benign course for a varying but limited period before it transforms into a more acute type of leukemia or blast crisis. At this point the patient deteriorates rapidly and dies within a short time. Between 1975 and May 1988, 230 patients with CML have been followed at KFSH. Of these, 92 are known to have developed blastic transformation including myelofibrosis (MF). By a variety of modalities the blast crises have been characterized as follows: myeloid, 26; lymphoid, 29; AMMol, 6; AMol, 3; APL, 1; ERY, 1; MGK(MF), 14; mixed, 9; and unclassified, 3. We examined the potential of using monoclonal antibodies to trace the lineage of blast cells in CML as the disease evolves from the chronic phase to blast crisis.

BLOOD BANK SUPPORT OF ABO-INCOMPATIBLE BONE MARROW TRANSPLANTATION, J Schifano, S Bernvil, King Faisal Specialist Hospital and Research Centre, Riyadh

Bone marrow transplant candidates receive irradiation and cytotoxic drugs which destroy the endogenous marrow and cause temporary aplasia. Transfusion support is necessary during the post-transplant period until sufficient erythroid engraftment occurs. Although the ABO blood group does not constitute a risk factor for successful engraftment, ABO-incompatible transplants do require substantial blood bank support. The foremost complication of a major ABO incompatibility (recipient antibody against donor red cells) is hemolysis of the donor cells at the time of marrow transplantation. However, this may be effectively prevented by either plasma exchange of the recipient or removal of donor red blood cells from the marrow before infusion. The preferred method in our blood bank involves centrifugation of the bone marrow harvest with subsequent depletion of the red cells. Additional long-term effects of major ABO-incompatible bone marrow transplantation include delayed engraftment and increased requirements for homologous red cells. Fortunately, these sequelae have not affected patient morbidity and mortality.

THE GEOGRAPHY OF SICKLE CELL DISEASE, GR Serjeant, University of the West Indies, Kingston, Jamaica

The occurrence of homozygous sickle cell (SS) disease in different geographic areas offers an opportunity to study the effects of different environmental and genetic factors on its expression. Studies of polymorphisms suggest that the HbS mutation has arisen on at least four independent occasions, three in West and Equatorial Africa (Senegal, Benin, and Bantu haplotypes) and once in Saudi Arabia/India (Asian haplotype). The latter haplotype is linked to high levels of HbF, which inhibits sickling resulting in high hemoglobin levels, persistence of splenomegaly, and relative infrequency of vaso-occlusive complications. The Senegal haplotype, if inherited homozygously, may also be linked to high HbF levels and a mild course although the evidence is much less compelling than with the Asian haplotype. In both African and Asian areas, SS disease is associated with a high frequency of deletional alpha-thalassemia which is rare among SS populations in Northern Greece and Sicily. Comparative studies may contribute to an understanding of the pathophysiology of SS disease.

PARVOVIRUS AND THE ANAPLASTIC CRISIS, GR Serjeant, BE Serjeant, MJ Anderson, University of the West Indies, Kingston, Jamaica, and University College Hospital, London, England

Aplastic crises are sudden and temporary episodes of predominantly erythropoietic arrest. When occurring in patients with shortened red cell survival, there may be a rapid fall in hemoglobin levels to life-threatening levels. The epidemic nature of aplastic crises, their familial involvement, and preceding symptoms of upper respiratory tract type infection all suggested that these episodes were infective in origin. The human parvovirus is now recognized to be responsible for the great majority of these events. In Jamaica, it has been possible to study the last three epidemics of aplastic crises in homozygous sickle cell (SS) disease, the 1973-1975 epidemic retrospectively, and the 1979-1981 and 1984-1987 epidemic prospectively. Evidence of concurrent parvovirus infection was obtained in 13/13 (100%), 44/45 (98%), and 84/90 (93%) of the three epidemics, respectively. The human parvovirus has therefore been the dominant but not the only cause of clinically defined aplastic crises over the last 15 years in Jamaica.

CHROMOSOMAL ABNORMALITIES IN HEMATOLOGIC MALIGNANCY, KV Sheth, King Faisal Specialist Hospital and Research Centre, Riyadh

High-resolution and G-band techniques in chromosomal analysis for hematologic malignancies have shown certain patterns of reciprocal translocations, inversions, duplications, deletions, and several numeric chromosomal abnormalities. At the same time, a group of proto-oncogenes has been discovered, each of which, when altered, has been implicated in transforming normal into neoplastic cells in vitro. These oncogenes, which were first identified in neoplastic tissues and thought to be distributed by retrovirus, occur in all human eukaryocytes. More than 30 oncogenes have been identified, with 28 of them already mapped in the human karyotype. Protein products of the various oncogenes are very similar to known normal growth factors, to proteins which allow transmembrane transduction of exogenous signals, and to nuclear-DNA binding substances, so now oncogenes are regarded as playing vital roles in normal cell growth and differentiation. Like all other genes, if an oncogene is mutated, rearranged, translocated, or deleted, its effects change, and it produces disorderly, uncontrolled cell proliferation and differentiation possibly resulting in neoplasia. At KFSH&RC, high resolution and G-banding techniques have shown Philadelphia translocation in all 188 cases of adult chronic myeloid leukemia. The Philadelphia translocation is a reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 22. The breakpoint occurs at a small precise point, known as the breakpoint cluster region (bcr). The hybrid bcr/abl gene transcribes into protein of p210 KD, which plays a role in phosphorylation of protein kinase C. The chromosomal break results in derangement of oncogene function, which translates into neoplasia.

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) AND METHICILLIN-RESISTANT *S.EPIDERMIDIS* (MRSE). AM Shibl, King Saud University, Riyadh

Both MRSA and MRSE continue to be leading causes of nosocomial infections in hospitals, and the infections that they cause require specialized chemotherapy. There is need for a sensitive, standardized procedure for the detection of the methicillin-resistant phenotype in the clinical laboratory. Modification in test methods that favor phenotypic expression of methicillin resistance include such factors as large inoculum, incubation at lower temperature, prolonged incubation, and salt content in the medium. Recent surveillance in Riyadh hospitals demonstrated that 5% of *S. aureus* and 30% of *S. epidermidis* isolates were resistant to methicillin. The present study was undertaken to evaluate several methods recommended for the detection of methicillin-resistant phenotype of both *S. aureus* and *S. epidermidis*. The number of methicillin-resistant strains detected was higher in Mueller-Hinton agar medium supplemented with salt. The in vitro susceptibility of local clinical isolates of MRSA and MRSE to several agents was compared. Vancomycin remains the antibiotic of choice in the treatment of serious infections caused by MRSA and MRSE. Combinations of rifampin and fusidic acid are also useful in certain clinical cases caused by susceptible strains of MRSA. Recently, additional agents have been shown to inhibit MRS such as coumermycin, the new fluorinated carboxyquinolines, teicoplanin, imipenem, and LY146032. Clinical experience in treating serious staphylococcal infection with these agents is limited. The present study leads to two suggestions for clinical laboratories. First, laboratory staff should be aware of clinical significance of an MRSA culture report and the potential of such a report to affect patient care. Second, laboratories with less experience in identifying MRSA and MRSE should review their technique and periodically reinstruct staff members.

AUTOLOGOUS BONE MARROW AND PERIPHERAL BLOOD STEM CELLS AFTER HIGH-DOSE CHEMORADIOTHERAPY FOR TREATMENT OF AML, DG Spence, for the Bone Marrow Transplant Team, King Faisal Specialist Hospital and Research Centre, Riyadh

High-dose chemoradiotherapy (HDCRT) in remission, followed by allogeneic bone marrow rescue from a fully compatible donor, may cure approximately 50% of AML patients under the age of 40. The procedure is limited, however, to those who have such a donor. Twenty percent relapse, and 30% die of transplant-related complications—graft-versus-host disease, pneumonitis, and opportunistic infections. Autologous stem cells of bone marrow origin may be harvested in remission and used as bone marrow rescue after HDCRT for patients lacking a donor. Autologous BM may, however, contain residual leukemic cells. Approaches to minimize the risk of recontamination include in vitro purging of bone marrow by chemicals or antibodies, long-term BM culture, or the use of stem cells harvested from peripheral blood early in first remission. Eleven ABMT procedures have been performed at KFSH: seven in CR1 (six alive), two in CR2 (one alive), one in relapse, and one in myelodysplastic remission. Two of 11 have relapsed. Six PBSC rescue procedures have been performed: two in CR1, three in CR2, and one in myelodysplastic remission. Three of six are alive and in remission. Median follow-up for ABMT patients is 20/12 and for PBSC patients is 10/12. Thirteen of 18 allografted AML first remission patients remain alive at median 15/12. Stem cells of autologous origin allow HDCRT to be used for AML patients without donors and avoid some of the morbidity of allogeneic BMT. It is to be expected, however, that more relapses will be seen in the autologous group, and it remains to be seen whether the use of PBSC instead of BM reduces the risk of relapse.

Poster Presentations

FINE-NEEDLE ASPIRATION BIOPSY OF SEMINOMA AND DYSGERMINOMA: CYTOLOGIC, HISTOLOGIC, AND ELECTRON MICROSCOPIC CORRELATIONS, M Akhtar, MA Ali, M Bakry, M Huq, King Faisal Specialist Hospital and Research Centre, Riyadh

Cytomorphologic features in a series of fine-needle aspiration biopsies from eight patients with seminoma/dysgerminoma were reviewed, and these findings were further correlated with histopathologic and ultrastructural appearances. Three cell types were encountered. Type I cell was least differentiated and was least frequent. Type II cell was most frequent and had well-developed cytoplasm which was rich in organelles. Type III cell was similar to type II cell but in addition contained large punched-out cytoplasmic vacuoles corresponding to the areas of glycogen deposition. The background contained a variable mixture of inflammatory cells including lymphocytes, plasma cells, epithelioid cells, and epithelioid granulomas. The significance of these findings in the diagnosis of seminoma/dysgerminoma and its distinction from other germ cell and non-germ cell tumors was briefly discussed.

FINE-NEEDLE ASPIRATION BIOPSY DIAGNOSIS OF ENDODERMAL SINUS TUMOR, M Akhtar, MA Ali, K Sackey, D Jackson, M Bakry, King Faisal Specialist Hospital and Research Centre

Fine-needle aspiration biopsies from five patients with endodermal sinus tumor were reviewed, and the findings were correlated with histologic and ultrastructural appearances. In the aspiration smears, two types of tumor cells were seen forming clusters of variable sizes. Type A cells had distinct cell borders, and their cytoplasms contained only occasional clusters. Type B cells had ill-defined cell borders and formed syncytial clusters. Their cytoplasm was characterized by large numbers of rounded vacuoles. The background contained patches of mucoid material and macrophages with foamy cytoplasm. Eosinophilic hyaline cytoplasmic bodies and irregular deposits of intercellular basement membrane-like material were recognized easily in aspiration smears. These features correlated well with histologic and ultrastructural appearances. The significance of these findings in the fine-needle aspiration biopsy diagnosis of endodermal sinus tumor and its distinction from other germ cell and non-germ cell tumors were discussed.

MORPHOLOGICAL AND IMMUNOPATHOLOGICAL SPECTRUM OF MALIGNANT LYMPHOMA AT KING FAISAL SPECIALIST HOSPITAL: REVIEW OF 211 CASES, MA Ali, M Akhtar, M Amer, KP Yri, King Faisal Specialist Hospital and Research Centre, Riyadh

A series of 211 malignant lymphomas in adults was reviewed and classified according to the international working formulation. There were five low-grade (2.4%), 115 intermediate-grade (54.5%), and 85 high-grade lymphomas (40.3%). Immunohistologic typing of 106 lymphomas was performed using a panel of monoclonal antibodies against T- and B-cell surface antigens. This revealed 51 (49%) B-cell and 41 (38%) T-cell lymphomas with 14 (13%) indeterminate. These results were compared with those from several recently published studies from other countries. There appeared to be a relatively high proportion of aggressive lymphomas in our series. Furthermore, immunohistologic data in our study indicated a significantly higher proportion of T-cell lymphomas as compared to other studies.

ASPIRATION CYTOLOGY OF NASOPHARYNGEAL CARCINOMA: CYTOLOGIC AND HISTOPATHOLOGIC CORRELATIONS IN 30 CASES, MA Ali, M Akhtar, A Burgess, King Faisal Specialist Hospital and Research Centre, Riyadh

Fine-needle aspiration biopsy specimens from 30 histologically confirmed cases of nasopharyngeal carcinoma were reviewed, and findings were correlated with corresponding histopathologic appearance. Twenty-five biopsies were from cervical lymph nodes and one each from axilla, scalp, mediastinum, chest wall, and liver. Smears were air-dried and stained with Diff-Quik stain. In the aspiration smears, a majority of the tumor cells were arranged in tight clusters and sheets with few single cells. These cells varied from round to polygonal and spindle in shape and could be divided into small, intermediate, and large cells. Nuclei in small cells were uniform and round with a fine chromatin pattern and inconspicuous nucleoli. The nuclei in the intermediate cells were more pleomorphic and revealed one or more well-formed nucleoli. The large cells contained nuclei with significant pleomorphism and usually prominent nucleoli. Clusters of naked nuclei were also seen in many smears. In the background granulomas were present in 10 cases, numerous histiocytes in six cases, while small lymphocytes and immunoblasts were present in six cases. Histologic classification (WHO) of the tumors revealed nonkeratinizing squamous cell carcinoma in 26 cases and undifferentiated carcinoma in four. No case of keratinizing squamous cell carcinoma was encountered. Correlation of histologic and cytologic features revealed that the smears from undifferentiated carcinoma were characterized by cells with large ballooned, pale-staining nuclei with prominent inclusion-like nucleoli. Lack of these features indicated a nonkeratinizing squamous cell carcinoma. The study indicated that fine-needle aspiration biopsy may be used successfully for diagnosis and classification of nasopharyngeal carcinoma.

RAPID IDENTIFICATION AND DRUG SUSCEPTIBILITY TESTING OF MYCOBACTERIA BY A RADIOMETRIC METHOD, L Brodie, M Burdette, G Lee, SMH Qadri, King Faisal Specialist Hospital and Research Centre, Riyadh

Ability of mycobacteria to cause serious disease in humans and their tendency to develop resistance to antimycobacterial drugs make it necessary to identify them and perform susceptibility testing. Conventional methods are both cumbersome and time-consuming, requiring as much as 6 weeks. We recently evaluated the Bactec 460, which is both rapid and relatively simple. The identification involves the use of NAP (*P*-nitro-a-acetylamino-B-hydroxy-propiophenone), which inhibits mycobacteria belonging to the TB complex: *M. tuberculosis*, *M. bovis*, *M.africanum*, and *M. microti*, while others show either slight or no inhibition. After initial isolation, only 4 to 6 days are necessary. Initially, comparative studies between KFSH&RC and the Mycobacteria Reference Unit in Cardiff, Wales, were performed on 50 isolates. Fourteen percent of these were identified in both labs as *M. tuberculosis*. One isolate failed to grow both here and in Wales, while the remaining 42 isolates were identified in both labs as MOTT, showing 100% correlation. The Bactec can also be used for drug susceptibility testing. Instead of counting colonies after 21 to 28 days incubation in the conventional method, the growth in Bactec system is monitored radiometrically, yielding results in 4 to 8 days. A comparison of susceptibility results using seven isolates of *M. tuberculosis* at KFSH&RC and the reference laboratory showed 100% correlation. In addition, our studies of *M. tuberculosis* isolates to second line drugs (such as rifampin, ethambutol, and amikacin) using Bactec system have provided valuable information in patient management. We found the radiometric method to be rapid and reliable, resulting in more efficient service.

MEASUREMENT OF PLATELET-ASSOCIATED IMMUNOGLOBULINS BY USE OF MONOCLONAL ANTIBODIES IN A FLOW CYTOMETRY SYSTEM, G Damanhouri, R Elmes, GT Roberts, King Faisal Specialist Hospital and Research Centre, Riyadh

Demonstration and measurement of platelet-associated immunoglobulins (PAIG) in patients with thrombocytopenia due to immune destruction have been tedious and difficult processes. Recently, PAIG has been measured successfully using immunoradiometric assays. This method has the obvious disadvantages associated with the use of radioactive substances. Since 1983 we have been using FITC conjugated mouse monoclonal antibodies against human immunoglobulin G and M to tag platelets in patients with thrombocytopenia and measuring the fluorescence in a Coulter Epics V flow cytometer. This method has been useful and is able to identify PAIG in patients with immune thrombocytopenia, although as previously reported, PAIG is also demonstrable in some patients without definite immune thrombocytopenia. In patients with nonimmune thrombocytopenia, our results have always been negative for PAIG.

PREPARATION OF PACKED RED CELLS SUITABLE FOR INTRACARDIAC TRANSFUSION IN UTERO, B Galligan, R Cairns, J Schifano, S Bernvil, King Faisal Specialist Hospital and Research Centre, Riyadh

In the Middle East, erythroblastosis fetalis due to Rh isoimmunization is not uncommon. In our hospital, we see approximately 50 new cases a year, many of whom are treated several times during the pregnancy with intrauterine transfusion. Intracardiac transfusion has recently been proposed as an alternative route to intraumbilical cord transfusion. The procedure has been described as having a high risk of complication characterized by bradycardia and cardiac arrest. Intracardiac hyperkalemia was suspected as being a major contributing factor toward the complications experienced. The procedure is warranted, however, in cases where intraumbilical cord transfusion is not possible. Therefore, studies comparing various methods of preparing packed cells for intracardiac transfusion were initiated. The potassium levels of gravity sedimented packed cells and saline-washed red cells resuspended in Ringer's lactate, pooled donor plasma, or saline were measured. Saline-washed/resuspended packed red cells transfused within 2 hours of preparation gave low potassium levels while exposing the fetus to minimal disease risk and were therefore selected to be the most suitable product. Using this product, the obstetricians observed a dramatic decrease in the incidence of bradycardia and cardiac arrest in 25 procedures.

CYTOCHEMISTRY IN THE DIAGNOSIS OF MALIGNANT HEMATOLOGICAL DISEASE, JA Huebner, GT Roberts, King Faisal Specialist Hospital and Research Centre, Riyadh

A number of cytochemical procedures are now available which facilitate the diagnosis and classification of hematologic malignancies. Most of the procedures are simple, but they require attention to details of timing, pH, and temperature; if done correctly, they provide very useful information. We outlined some of the typical reactions of Sudan black, myeloperoxidase, PAS, esterases, and acid phosphatases, and illustrated how they help in diagnosis and classification.

NORMAL RANGE FOR BONE MARROW DIFFERENTIAL CELL COUNTS IN SAUDI ARABIANS, S Khalil, F Mohareb, GT Roberts, King Faisal Specialist Hospital and Research Centre, Riyadh

The decision as to whether a patient being treated for acute leukemia is in remission from disease is based partly on the demonstration that less than 3% to 5% of blast cells are present in aspirated bone marrow smears. This criterion has been developed from experience in treating Western patients and also on normal ranges determined from study of bone marrow in hematologically normal Western subjects. There are environmental and probably general reasons why the normal ranges described for Western subjects may not apply for Saudi Arabian subjects. We therefore studied the normal values for bone marrow cell differential counts in normal Saudi Arabian donors of bone marrow for their siblings undergoing allogeneic bone marrow transplant for malignant and nonmalignant hematologic disease. In 18 such normal donors, we found the following ranges (%) for the cell types indicated: blasts, mean 0.3, SD 0.2; promyelocytes, mean 1.2, SD 0.5; segmented neutrophils, mean 25.8, SD 6.8; lymphocytes, mean 23.1, SD 7.4; monocytes, mean 5.9, SD 2.3; proerythrocytes, mean 0.5, SD 0.4; and megakaryocytes, mean 0.2, SD 0.1.

IN VITRO ACTIVITY OF IMIPENEM AND ITS COMPARISON WITH OTHER ANTIBIOTICS AGAINST 1400 CLINICAL ISOLATES, SMH Qadri, A Al-Hosain, S Ostrawski, King Faisal Specialist Hospital and Research Centre, Riyadh

Imipenem is a new carbapenem antibiotic with an excellent antibacterial activity against gram-positive as well as gram-negative bacteria, aerobes as well as anaerobes. Almost all of the previous studies were confined to bacterial strains isolated in North America or Europe where organisms are known to be more susceptible to commonly used antibiotics than the ones isolated in Asia, Africa, and South America. Our past studies have shown that bacterial isolates at KFSH&RC and Riyadh Central Hospital are significantly more resistant than their counterparts in the USA. We reported the in vitro activity of imipenem against clinical isolates at KFSH&RC. The bacteria used in this study consisted of *Escherichia coli* (329), *Klebsiella pneumoniae* (118), *K. oxytoca* (11), *Pseudomonas aeruginosa* (194), *Pseudomonas* sp. (17), *Proteus* sp. (68), *Enterobacter agglomerans* (8), *E. cloacae* (157), *Enterobacter* sp. (12), *Citrobacter* sp. (15), *Acinetobacter calcoaceticus* (17), *Providencia* (6), *Morganella* (6), *Serratia* (41), *Shigella* (5), *Salmonella* (52), *Aeromonas* (6), staphylococci (242), streptococci (98), *Bacillus* (7), *Bacteroides* (28), *Fusobacterium* (8), *Clostridium* (17), peptococci (14), and *Propionibacterium* (22). Antibacterial activity of imipenem was compared with other commonly used antibiotics. All the isolates of Enterobacteriaceae, *S. aureus*, enterococci, and streptococci were inhibited by imipenem. The majority of the *P. aeruginosa* (95%) and *S. epidermidis* (90%) isolates were susceptible to imipenem, but all six isolates of *P. maltophilia* were resistant. In vitro activity of this carbapenem against anaerobic bacteria was comparable to metronidazole.

ANTIMICROBIAL RESISTANCE PATTERNS OF *ESCHERICHIA COLI*, *KLEBSIELLA PNEUMONIAE*, AND *PSEUDOMONAS AERUGINOSA*. SMH Qadri, WH Rizvi, S Ostrawski, F Al-Dayel, King Faisal Specialist Hospital and Research Centre, and Riyadh Central Hospital, Riyadh

In vitro resistance of 10,581 clinical isolates of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* to seven commonly used antibiotics was determined at the 1700-bed Riyadh Central Hospital (RCH) and 450-bed KFSH and compared with 5513 strains at the 450-bed Oklahoma Memorial Hospital (OMH) and 434-bed Veterans Administration Medical Center (VAMC) in Oklahoma City. Antibiotic susceptibility was determined by disk-diffusion test using amikacin, ampicillin, carbenicillin, gentamicin, piperacillin, trimethioprim/sulfamethoxazole, and tobramycin. Isolates of *E. coli* were more resistant (56% to 60%) to ampicillin at RCH and KFSH than at OMH (34%) or VAMC (38%). Similar results were obtained with all other antibiotics except amikacin, which was highly effective at all institutions. Resistance of *E. coli* to trimethioprim/sulfamethoxazole was four times higher at RCH and KFSH than at VAMC (12%) and eight times more than at OMH (6%). Sensitivity pattern of *K. pneumoniae* was very similar at RCH and VAMC, the organisms being more resistant to commonly used drugs than at KFSH and OMH. Resistance to gentamicin and trimethioprim/sulfamethoxazole was significantly higher at VAMC than at RCH or KFSH. Pseudomonads in general showed a higher degree of resistance in Saudi Arabia than in the United States, 41% to 57% being resistant to carbenicillin and 34% to gentamicin in Saudi Arabia, whereas the resistance rate for these antibiotics in the United States was 20% and 14%, respectively. Resistance to tobramycin at RCH (28%) was four times higher than at OMH (6%) and VAMC (7%).

DELETERIOUS EFFECTS OF RED CELL PRODUCTS ON PLATELET COUNTS IN THROMBOCYTOPENIC PATIENTS, J Schifano, B Galligan, P Ernst, D Spence, S Bernvil, King Faisal Specialist Hospital and Research Centre, Riyadh

Microaggregates in stored red cell products have been implicated in post-transfusion thrombocytopenia. Adherence of endogenous platelets to the infused microaggregate debris results in increased splenic sequestration. This complication of routine red cell transfusions is especially serious in thrombocytopenic patients. Therefore, a red cell product depleted of microaggregates may be necessary to avoid causing even lower platelet counts and possible hemorrhage. This study compared transfusion (2 units) of either packed red cells through a 170-μ filter or "spin-filtered" packed red cells through a 40-μ filter. Thirty-seven patients with hematologic malignancies comprised the study group; they were 14 to 60 years of age and had a pretransfusion platelet count of 30 to 70 × 10^9/L. The peripheral platelet count was measured immediately before red cell transfusion and at 1 and 6 hours after the second unit was infused. Initial study results indicated that spin-filtered packed red cells given to 19 patients were significantly ($P < 0.01$) less likely to exacerbate thrombocytopenia than routine packed red cells given to 18 patients.

A MONOCLONAL ANTIBODY AGAINST HUMAN TUMOR ANTIGENS, SBT Al-Sedairy, King Faisal Specalist Hospital and Research Centre, Riyadh

The LC1 is an IgM type MoAb produced by fusion of myeloma cell line (NS1) with spleen cell of mice immunized with human lung carcinoma cell line (ChaGO). This MoAb recognizes a 330 kd/310 kd glycoprotein antigen complex. The tissue distribution of the antigen recognized by MoAbLC1 was analyzed immunohistochemically with a large panel of normal and neoplastic human fixed tissues. The LC1 reacted with all histologic types of lung tumors tested (adeno large cell, neuroendocrine, squamous, small cell, and bronchioalveolar carcinomas); it was also reactive with normal alveoli and/or bronchiepithelial cells. In a panel of nonpulmonary tumors tested, LC1 reacted with transitional cell carcinoma of the urinary bladder, mucoepidermoid carcinoma of the parotid gland, while negative to the pancreas, prostate, breast, esophagus, colon, ovary, thyroid, stomach, renal cell carcinoma, malignant melanoma, Hurthle cell adenoma of the thyroid, and hepatomas. MoAbLC1 reacted with normal skin sebaceous gland, normal thyroid follicular cells, and parotid gland ductal epithelium. MoAbLC1 reacted with fetal tissues of lung and kidney and of cytotrophoblast and epithelial cells, although LC1 did not react with carcinoembryonic antigen or alphafetoprotein. These results suggest that the antigen is expressed widely by both normal and neoplastic lung cell, and its detection in other tissues is more limited.

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International Conference on Emergency Health Care Development

An International Conference on Emergency Health Care Development will be held in Washington, DC, 15-18 August 1989. The conference is being organized by Medical Care Development International in collaboration with the US Public Health Service, the Pan American Health Organization, the Federal Emergency Management Agency, the United Nations Disaster Relief Office, and other national and international organizations that deal with emergency health care issues.

The conference will focus on issues related to the development and upgrading of emergency health care services on a worldwide basis. The goal is to achieve a consensus on a world concept of emergency health care that is not limited to Western-oriented, technologically defined emergency medical services. It will examine methods of building and improving the ability of health care systems to respond to routine medical emergencies and to coordinate the additional resources needed for response to mass casualty incidents and disasters. The conference will address the organization of emergency health care in urban and rural areas of industrialized and developing countries. Representatives of international funding organizations will review potential methods of funding emergency health care system improvements. The faculty will include emergency health care specialists from outside the United States, and participants are expected to include representatives from many countries of the world.

The conference is open to all emergency health care professionals and planners/managers of health care services.

Information regarding the conference program or registration can be obtained from EHC Conference, MCD International, 1742 R St., NW, Washington, DC 20009, USA; telephone (202) 462-1920.

18th International Epilepsy Congress

The 18th International Epilepsy Congress is scheduled for 18-22 October 1989 in New Delhi, India. The scientific program will include presentations on primary health care and epilepsy, epilepsy and surgery, prognosis in epilepsy, and new developments in antiepileptic drug treatment. Special sessions will include a patient forum, an evaluation of the classification of epilepsies and epileptic syndromes, and discussion of epilepsy, genetics, pregnancy, and the child. For additional information, contact Professor M. C. Maheshwari, Secretary General (18th IEC 1989), Department of Neurology, Neuro-Sciences Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India.

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King Faisal Specialist Hospital and Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

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For further information contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

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King Saud University Hospitals (King Khalid University Hospital/King Abdul Aziz University Hospital) are pleased to invite applications for the following postgraduate training programs:

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3. Master's degree courses in pathology and family practice.
4. Residency training program in ophthalmology (in conjunction with King Khaled Eye Specialist Hospital).

For further information, contact the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P. O. Box 2925, Riyadh 11461, Saudi Arabia.

Second International Conference on Systemic Lupus Erythematosus

The National Arthritis Foundation of Singapore and the Society of Immunology and Rheumatology are organizing the Second International Conference on Systemic Lupus Erythematosus to be held 26-30 September 1989 in Singapore. The meeting will combine clinical and scientific plenary sessions, seminars, and free papers. For further details, contact Dr. P. H. Feng, Chairman, Organizing Committee, Second International Conference on SLE, Department of Medicine IV, Tan Tock Seng Hospital, Moulmein Road, Singapore 1130; telephone (65)-3508214; telex RS 39675 TTSH.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

1. Doctors who hold MB,BS from King Saud University or equivalent degree with at least Good grade.
2. Doctors who have finished their internship in a recognized hospital with at least a Very Good grade.
3. Successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the whole period of training.

Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Riyadh Armed Forces Hospital Symposia

The Armed Forces Hospital of Riyadh has announced the following calendar of upcoming symposia:

1. International Symposium on Advanced Medicine II, 17-19 September 1989.
2. Advances in Neurology and Neurosurgery, 1-2 October 1989.
3. Medical and Surgical Aspects of Hepatobiliary Disease, 19-20 November 1989.
4. Symposium on Atherosclerosis, 26-27 November 1989.
5. Modern Trends in the Management of Valvular Heart Diseases, 14-17 January 1990.

For additional information, contact the Department of Medical Studies, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia; telephone (01) 477-7714, extensions 2269, 3548, 3549, 3550; telex 401645 RKHPA SJ; telefax 477-9168.

King Faisal Specialist Hospital and Research Centre Symposia for 1410

King Faisal Specialist Hospital and Research Centre has scheduled the following postgraduate education symposia:

1. Health Care Manpower Symposium, 3-4 October 1989 (4-5 Rabi Al-Awal 1410).
2. Fourth Annual Radiology Symposium, 10-11 October 1989 (11-12 Rabi Al-Awal 1410).
3. Symposium on Preventive and Restorative Dentistry, 17-18 October 1989 (18-19 Rabi Al-Awal 1410).
4. Annual Pathology Symposium, 31 October-1 November 1989 (2-3 Rabi Al-Thani 1410).
5. Pharmacy Practice in Saudi Arabia: Current and Future Trends, 13-15 November 1989 (15-17 Rabi Al-Thani 1410).
6. Annual Neonatology Symposium, 28-29 November 1989 (30 Rabi Al-Thani-1 Jumada Al-Awal 1410).
7. Fine-Needle Biopsy Tutorial, 5-7 December 1989 (7-9 Jumada Al-Awal 1410).
8. Symposium on Malignancies in Childhood, 6-7 February 1990 (11-12 Rajab 1410).
9. Third Annual Symposium on Excellence in Nursing, 26-28 February 1990 (1-3 Shaban 1410).
10. Symposium on Nonsurgical Management of Low Back Pain, 10-11 March 1990 (13-14 Shaban 1410).

For additional information, please contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

Radiopharmaceuticals from King Faisal Specialist Hospital and Research Centre

King Faisal Specialist Hospital and Research Centre produces various radiopharmaceuticals at its Radionuclide and Cyclotron Operations facility with the aid of model CS-30 Cyclotron. These radiopharmaceuticals are produced according to international standards of good manufacturing practice. The Research Centre meets all the international standards of quality assurance and environmental safety with regard to radiopharmaceuticals.

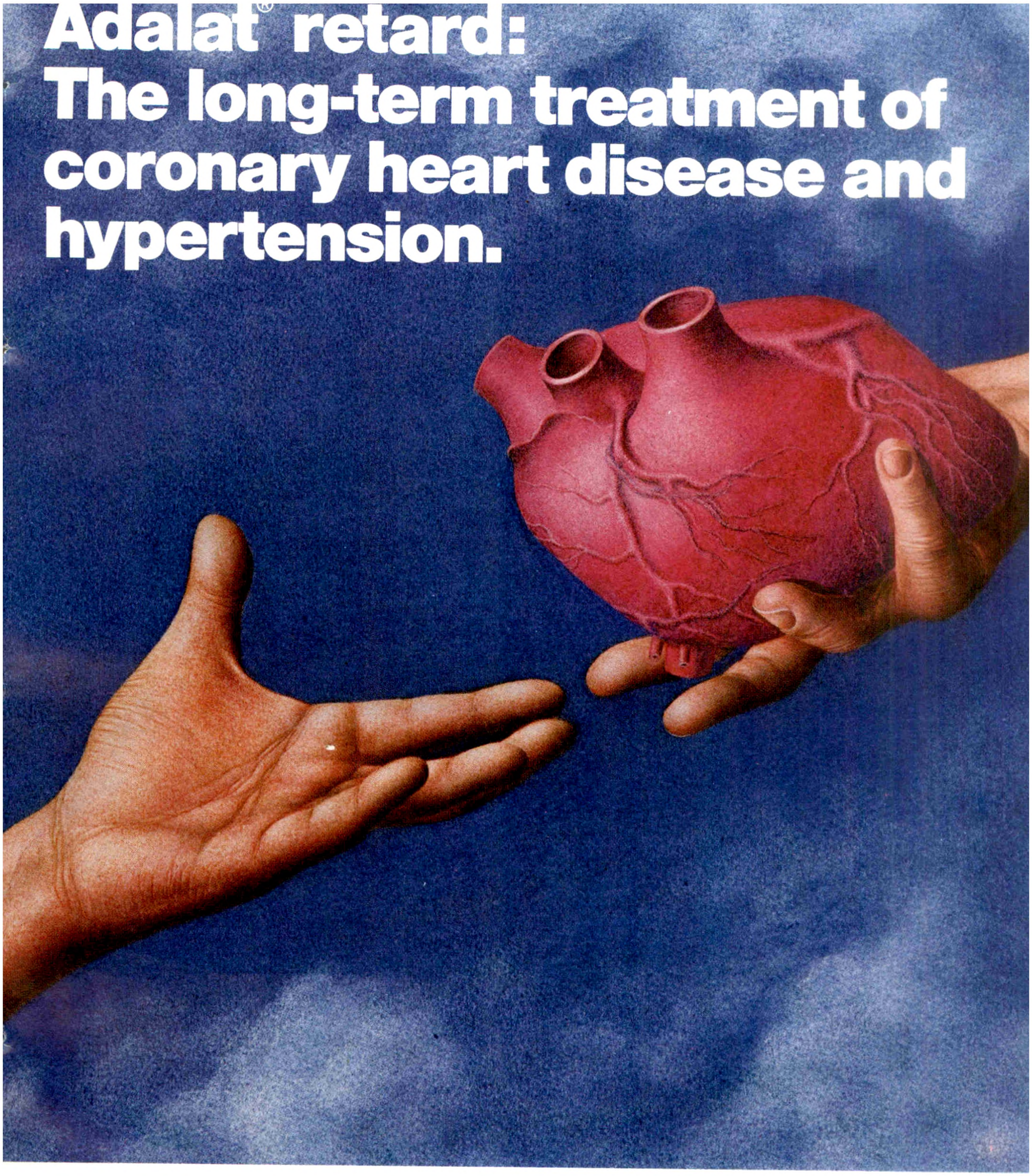
Radiopharmaceuticals currently produced and available for distribution throughout the Kingdom and to adjoining Arab states are as follows: thallous (Tl-201) chloride injection ($T^{1/2} = 73$ h); gallium (Ga-67) citrate injection ($T^{1/2} = 78.3$ h); iodine-123 capsules ($T^{1/2} = 13.1$ h); iodine-123 oral solution ($T^{1/2} = 13.1$ h); iodine-123 orthoiodohippurate solution ($T^{1/2} = 13.1$ h); rubidium (Rb-81) → krypton (Kr-81 m) generator ($T^{1/2} = 4.58 \text{ h} \rightarrow 13 \text{ s}$); indium (In-111) chloride injection ($T^{1/2} = 2.83$ d); and iodine-124 solution ($T^{1/2} = 4.17$ d).

Currently under development are indium (In-111) oxine for cell labeling; indium (In-111) DTPA for cisternography; I-123-labeled mIBG for imaging adrenergic tumors; and I-123-labeled fatty acids for evaluation of myocardial fatty acid metabolism. Suggestions from the medical community for additional radiopharmaceuticals are welcome.

Inquiries concerning the availability, price schedule, and technical information on specific radiopharmaceuticals should be directed to Abbass H. Al-Marzouky, MD, Executive Director, Research Centre, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 2900; telex 401050 ROSPEC SJ; telefax 464-7272, extension 1049.

IX Biennial International Congress of Cardiology

The Pakistan Cardiac Society has announced the IX Biennial International Congress of Cardiology to be held in Lahore, Pakistan, 7-10 December 1989. The official language of the program is English. For additional information, contact the Organizing Secretary, Congress Secretariat, Department of Cardiology, Mayo Hospital, Lahore, Pakistan; telephone (042) 310130, extension 13; telex 44516 HINON PK; telefax 92-42-871715.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Submission of Manuscripts. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. An abstract published prior to a full report is not regarded as a duplicate publication. The author's transmittal letter must accompany the manuscript and contain these statements: "The manuscript has been seen and approved by all authors involved and is neither being published nor being considered for publication elsewhere. The authors transfer copyright to the *Annals of Saudi Medicine*." Accepted manuscripts may not be published elsewhere without *Annals'* permission.

Manuscript Preparation. The format of the *Annals of Saudi Medicine* complies with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," published by the International Committee of Medical Journal Editors in Vancouver, British Columbia, in 1979 (the widely accepted "Vancouver style"), as described in the *Annals of Internal Medicine* (1982; 96 [pt 1]: 766-71). With the exception of blood pressure, all units of measurement and laboratory values must be expressed in SI units; conventional units may be included parenthetically. Authors are referred to *Annals of Internal Medicine* (1987;106[1]:114-29) for guidance in the use of SI units. Manuscripts, including tables, references, and figure legends, must be typewritten, double-spaced, on $8^1/_2 \times 11$ inch (21.5×28 cm) or size A4 paper, with margins of at least 1 inch (2.5 cm). Pages should be numbered consecutively, beginning with the title page and continuing through the last page of typewritten material. One original and two photocopies of the entire manuscript should be submitted, along with three sets of photographs.

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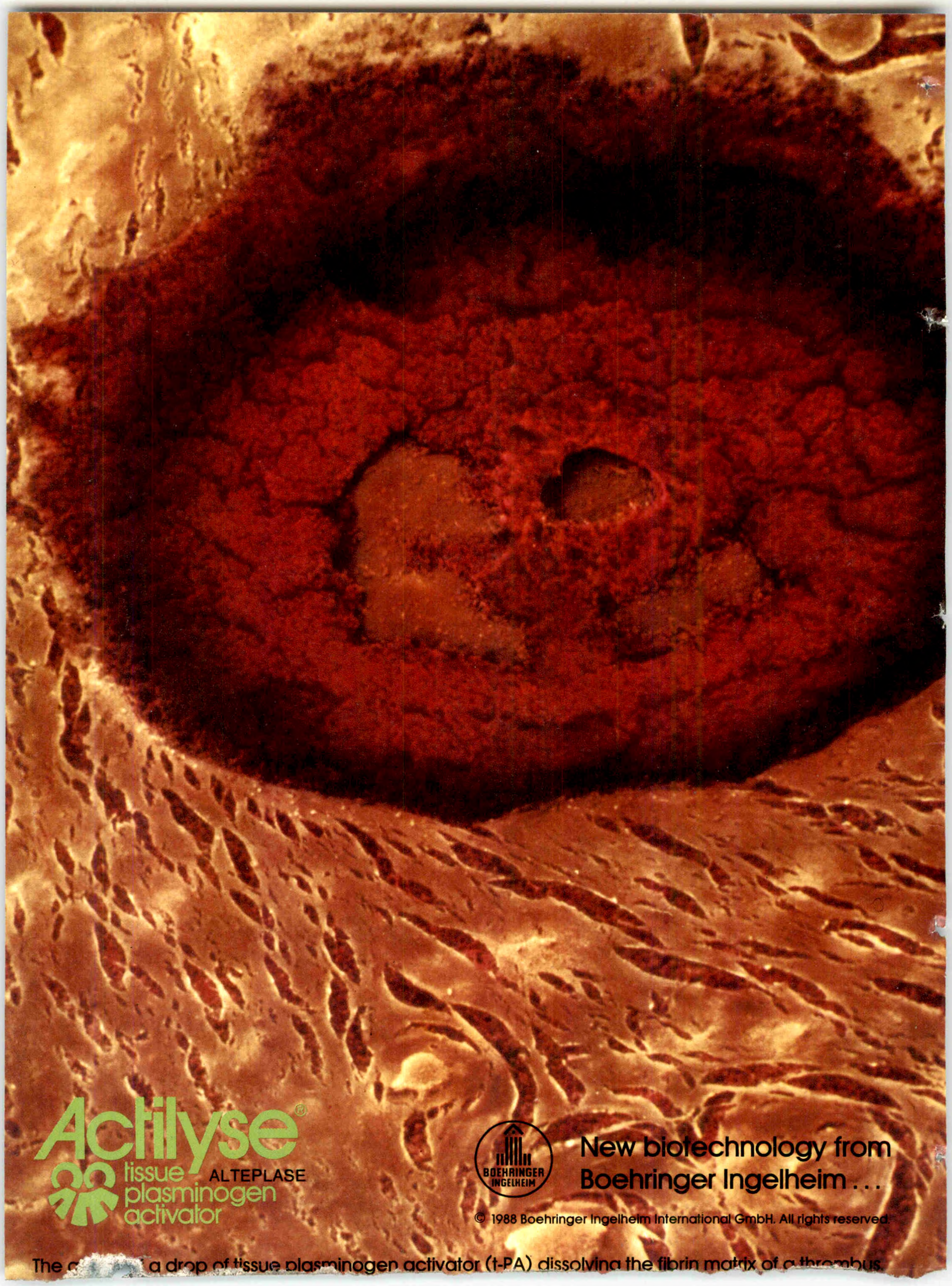

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ANNALS OF SAUDI MEDICINE

Aims and Scope

The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is typeset and printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal*, established in 1980.

The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers, written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

The *Annals* publishes original articles, case reports, letters to the editor, editorials, and from time to time, special communications, commentaries, and review articles. Abstracts of meetings and symposia sponsored by the Joint Board for Postgraduate Medical Education of Saudi Arabia are published, and the proceedings of such symposia may be published if the Editorial Board considers them appropriate and relevant. The Editorial Board wishes to minimize delay between manuscript submission, decision, and publication, and accordingly authors are requested to follow carefully the instructions set out under "Information for Authors."

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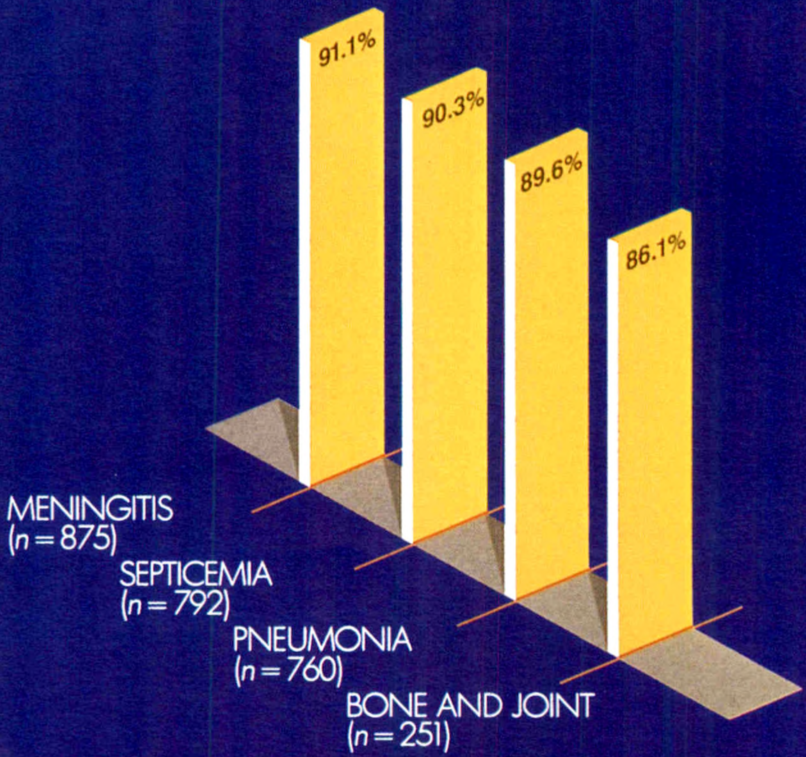

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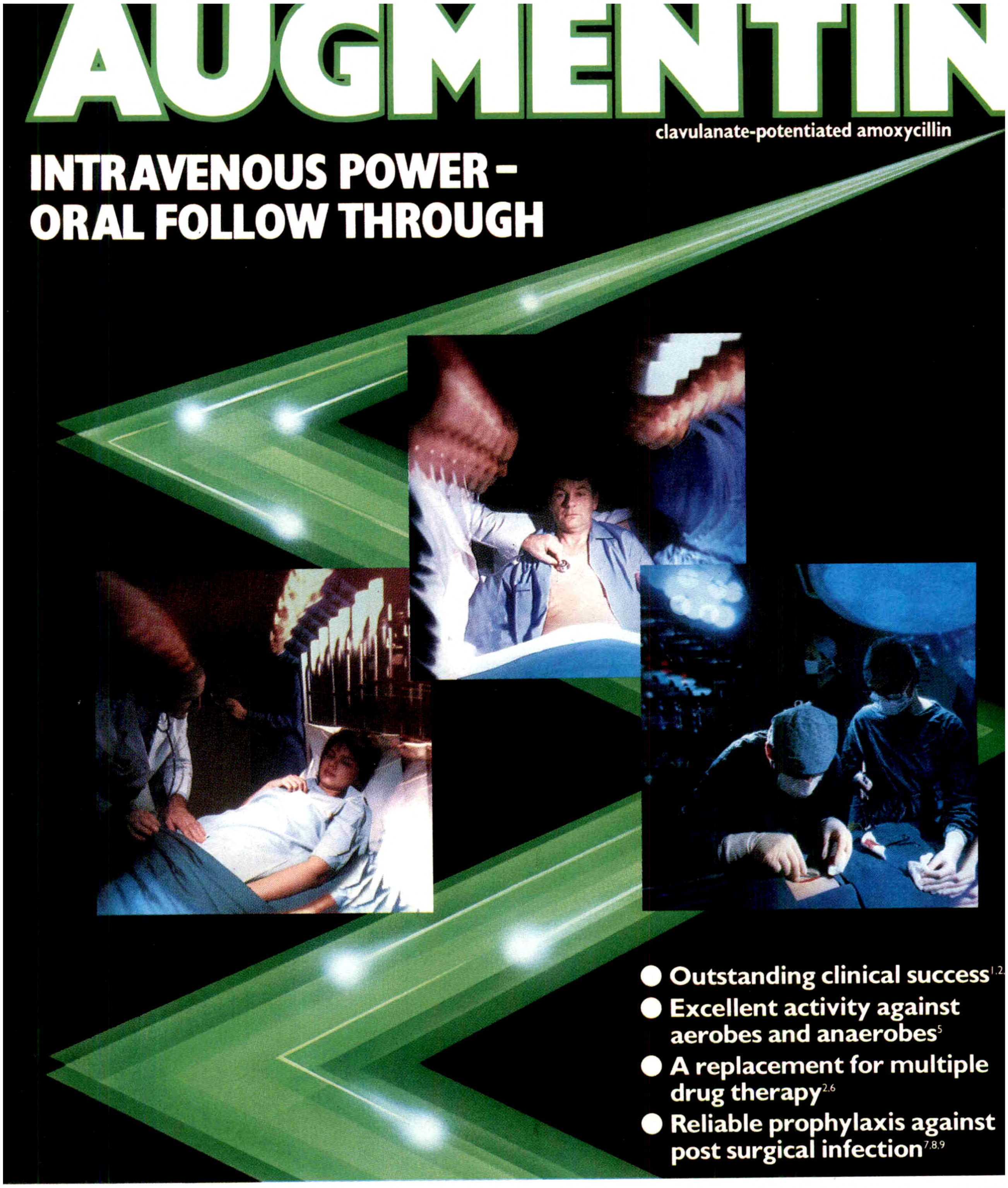
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References 1. Excerpta Medica, **CCP4**, (1983), 207. 2. J. Antimicrob. Chemother., (1982) **10**, (1), 67. 3. Proc. 4th Mediterr. Congr. Chemother. Rhodes, (1985), **4**, (2 suppl.): 199. 4. Excerpta Medica, **ICS 544**, (1980), 277. 5. Ibid.
6. Med. Int. (1983), (Suppl: Readings in Infections), 2. 7. Proc. 4th Mediterr. Congr. Chemother. Rhodes, (1985), **4**, (2 Suppl.), 776. 8. Br. J. Surg., (1985), **72**, (7), 571. 9. Proc. 26th ICAAC New Orleans, (1986), Abstr. 47

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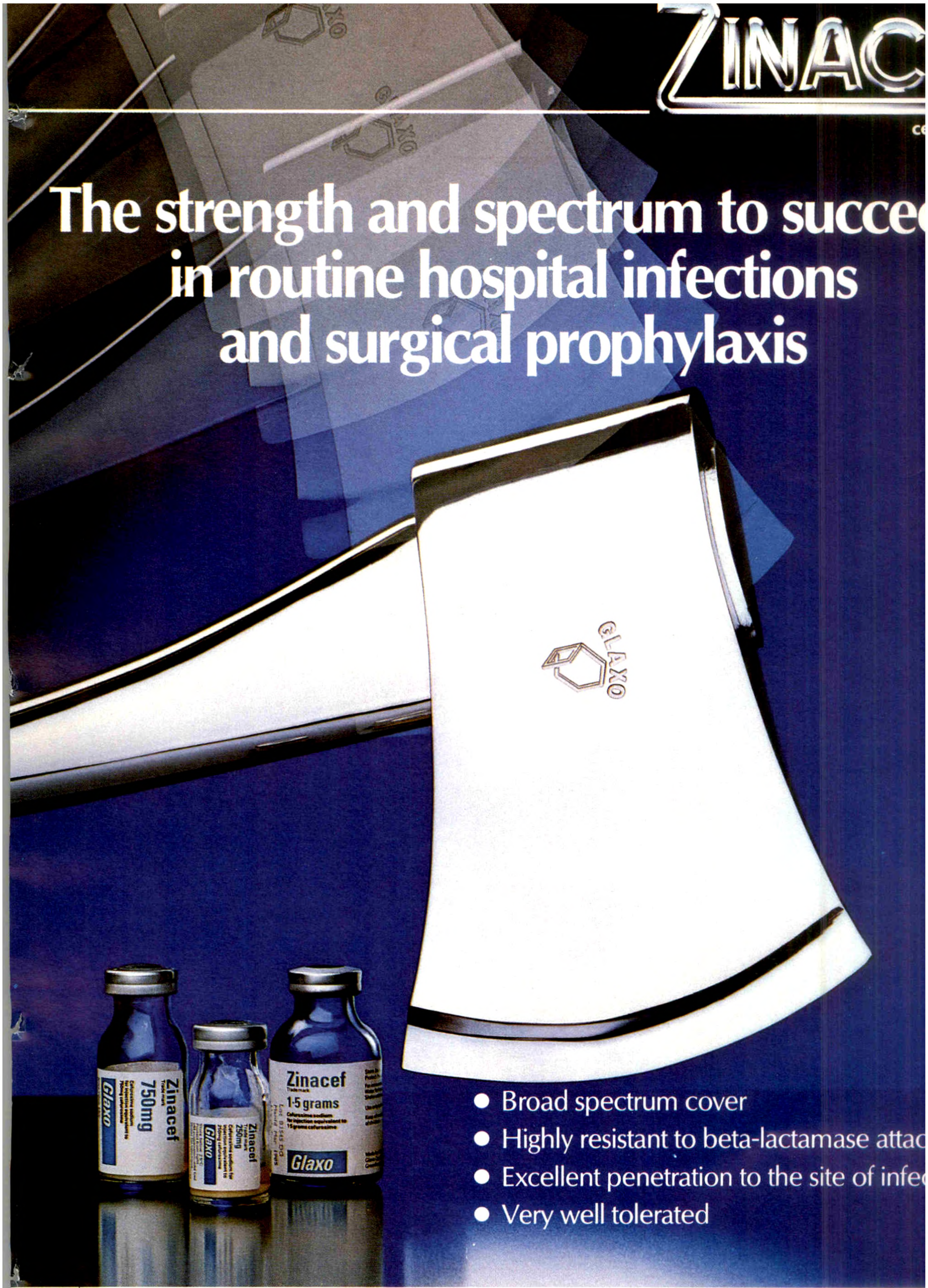

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1. DeBono, G.G. & Pearlgood, M., *Brit. J. Clin. Pract.*, 1986, **40** (10), 421. ORUVAIL is a Trade Mark. Further information is available on request from May & Baker Ltd., a division of Rhône-Poulenc, Dagenham, Essex RM10 7XS, UK.

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Submission of Manuscripts. Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. An abstract published prior to a full report is not regarded as a duplicate publication. The author's transmittal letter must accompany the manuscript and contain these statements: "The manuscript has been seen and approved by all authors involved and is neither being published nor being considered for publication elsewhere. The authors transfer copyright to the *Annals of Saudi Medicine*." Accepted manuscripts may not be published elsewhere without *Annals'* permission.

Manuscript Preparation. The format of the *Annals of Saudi Medicine* complies with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," published by the International Committee of Medical Journal Editors in Vancouver, British Columbia, in 1979 (the widely accepted "Vancouver style"), as described in the *Annals of Internal Medicine* (1982; 96 [pt 1]: 766-71). With the exception of blood pressure, all units of measurement and laboratory values must be expressed in SI units; conventional units may be included parenthetically. Authors are referred to *Annals of Internal Medicine* (1987;106[1]:114-29) for guidance in the use of SI units. Manuscripts, including tables, references, and figure legends, must be typewritten, double-spaced, on $8^1/_2 \times 11$ inch (21.5 × 28 cm) or size A4 paper, with margins of at least 1 inch (2.5 cm). Pages should be numbered consecutively, beginning with the title page and continuing through the last page of typewritten material. One original and two photocopies of the entire manuscript should be submitted, along with three sets of photographs.

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Abstracts. All original articles must contain an abstract of not more than 200 words. The abstract should include statements of problem, method of study, results, and conclusions.

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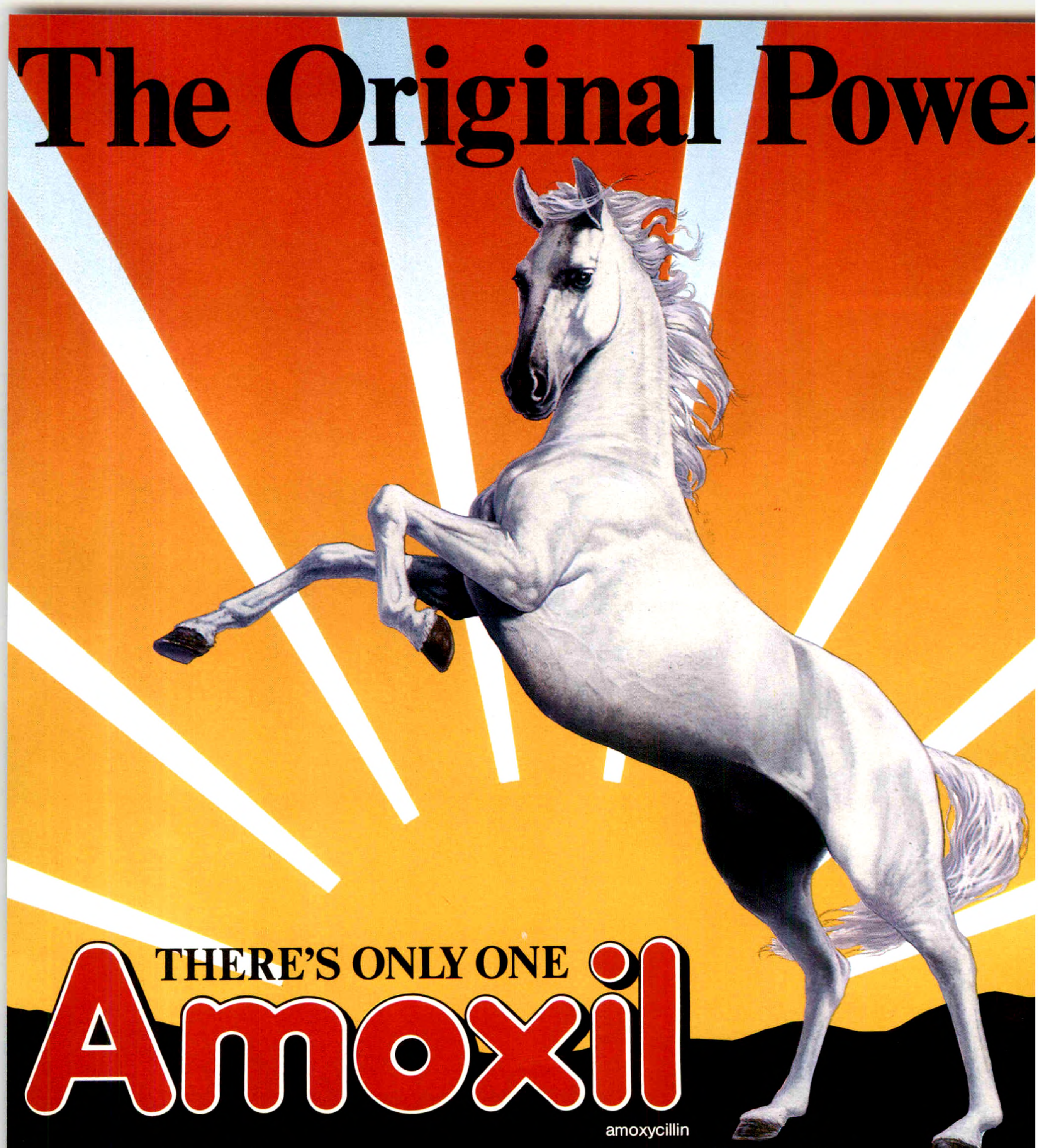

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Injection: Vials containing 250mg or 500mg amoxycillin as the s salt.
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| International Division 01/21

Editorial

REPORT FROM THE EDITOR

The *Annals of Saudi Medicine* is now in its ninth year of publication, having been founded in 1981 as the *King Faisal Specialist Hospital Medical Journal*. In 1985, the journal became a joint responsibility of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and was retitled the *Annals of Saudi Medicine*; soon after, all aspects of production were centralized in Saudi Arabia.

The objectives of the *Annals* continue to include the publication of high-quality papers on all aspects of medicine, particularly relating to medical and scientific practice in the Middle East where the combination of ancient traditions, ultramodern technology, rapid changes in the community, and continual striving for excellence provides a milieu which is unique. The *Annals* publishes original articles, clinical reviews, case reports, commentaries, editorials, letters to the editor, and proceedings of symposia, particularly those arranged by the Joint Board for Postgraduate Medical Education in the Kingdom of Saudi Arabia. As noted 3 years ago,[1] the *Annals* also provides an important forum for the publication of articles, letters, and other information relating to the developing undergraduate and postgraduate medical training programs in the Kingdom.

Initially produced four times a year, the *Annals* began bimonthly publication in January 1988 with Volume 8, Number 1. The increase to six issues per annum resulted in a decrease in publication "lag time" and a marked increase in the number of manuscripts submitted, from 206 in 1987 to 311 in 1988, up about 50%. Volume 8 (1988) included a total of 56 original articles and 25 case reports, also up about 50% from Volume 7 (1987). We expect to publish about 70 original articles and 30 case reports this year in Volume 9. The number of letters to the editor continues to increase, reflecting expanding dialogue between readers and authors as well as the wish of an increasing number of readers to share clinical, scientific, and ethical observations.

During the past few years, papers have been published from an increasingly wide number of institutions of broadening geographic location within the Kingdom, around the Middle East, and further afield. The quality of published papers has always been impressive, but with the increasing number of good submitted manuscripts, the Editorial Board has been able to improve the overall standard of published articles. All manuscripts are reviewed by the Editorial Board and by at least two independent reviewers, one of whom usually is an international authority in the field.

Some interested readers have commented on the relative frequency of papers being published from Riyadh compared with other centers in the Kingdom, and the relative infrequency of articles on particular medical or scientific topics. This simply reflects the range of papers being submitted—we can only publish from what we receive!

An informal direct-mail survey of our Saudi readers was conducted last year. *Annals* readers told us that in general they have access to some medical library facilities and regularly see about four international general medicine journals as well as one or two specialty journals. Features of the *Annals* favored by the majority were original articles, case reports, and symposium abstracts. Many expressed an interest to see more review articles. Already in 1989 and in the months to come we will strive to respond to these readers' interests, and we welcome constructive suggestions at any time.

The format of the *Annals* was changed a couple of years ago; and the layout continues to be improved. The Table of Contents appears on the outside back cover, and selected advertisements from international companies appear in each issue. The journal adopted SI units a year ago, and more recently has adopted an internationally accepted code of ethics relating to clinical research.

Over 14,000 copies of each issue now are distributed throughout the world, and the *Annals* is now listed in *Current Contents* and indexed in *Excerpta Medica.* We have applied for citation in other reference sources, including *Index Medicus*.

The *Annals* can only be as good as the material submitted, so we ask all readers to consider us as a journal of first choice for manuscripts of high medical and scientific interest.

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and Laboratory Medicine
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Riyadh 11211, Saudi Arabia

Reference

1. Herdson PB. Our fifth anniversary (editorial). Ann Saudi Med 1986;6(3):161.

Original Articles

INHALANT ALLERGENS IN PATIENTS WITH ALLERGIC RHINITIS IN RIYADH

Abdulaziz A. Al-Shalan, FRCS; Abdulrahman Al-Frayh, Facharzt;
Helen Reilly, NZCS; Khaled A. Al-Hussein, BSc; J. Douglas Wilson, FRACP, PhD

تم اختيار مجموعة كواشف الاختبار الجلدي للمستأرجات بتحديدها عن طريق دراسة الأحياء الهوائية والمناعيات الكيميائية وذلك لتجربتها في مرضى سعوديين ولمعرفة المستأرجات الكامنة في الجو وفي عينات غبار المنازل في منطقة الرياض. أظهر ثلثا مجموعة المرضى الذين شخصت اصابتهم سريريًا بالتهاب الأنف الآلرجي ايجابية لواحدة أو أكثر من مستأرجات الاختبار الجلدي. شملت قائمة كواشف الاختبار الجلدي التي حددت جميع مرضى الحساسية نبات رجل الوز، عشب برمودا، الهرة، الصرصور وسوس الغبار.

A group of allergen skin-test reagents were selected for study in Saudi patients from aerobiological and immunochemical identification of potential allergens in the atmosphere and from dust samples of Saudi homes in the Riyadh region. Two thirds of a group of patients diagnosed clinically with allergic rhinitis were positive to one or more of the skin-test allergens. A minimal skin-test panel which identified all atopic patients included Chenopodiaceae, Bermuda grass, cat, cockroach, and dust mite.

Intensive analysis of allergies in Saudi patients is a recent study, and the issue is complicated by the rapidly changing nature of the Saudi environment with introduction of extensive imported flora: agricultural, domestic, and ornamental, which contribute an increasing load of potentially allergenic pollen and contaminating fungal spores. The selection of allergens for skin-testing patients in any region of the Kingdom has, to date, been based on educated guesswork as to which potential allergens might be present in the patients' environment. But a definitive, comprehensive range of skin-test allergens can only be determined after the various species of flora releasing pollen, fungi, insects, animal danders, and other allergens actually present have been established.

A three-city study of allergens in Saudi Arabia using aerobiological screening of pollen and fungal spores in the atmosphere, culture, and immunochemical analyses of domestic dust samples has, over the past 2 years, identified a catalogue of potentially allergenic material in the Saudi environment.[1-3] While these studies are not yet complete for Jeddah and Al-Khobar, the Riyadh data have been used to select the most commonly appearing allergens to skin-test a group of patients identified clinically with a diagnosis of allergic rhinitis. The strategy has been first to identify the most common potential allergens, and then to examine which of these are stimulating IgE-mediated sensitivity in patients to determine a screening battery of allergens for skin-testing Saudi patients.

Patients and Methods

Ninety-six patients with a clinical diagnosis of allergic rhinitis were identified at the Ear, Nose and Throat Department of King Abdulaziz Uni-

---

From the Department of Otolaryngology, King Abdulaziz University Hospital (Dr. Al-Shalan); Department of Pediatrics, College of Medicine, King Saud University (Dr. Al-Frayh); and Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Centre (Ms. Reilly, Mr. Al-Hussein, and Dr. Wilson), Riyadh.

Address reprint requests and correspondence to Dr. Al-Frayh: Department of Pediatrics, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Accepted for publication 23 November 1988.

TABLE 1. *Patient characteristics.*

	Allergic rhinitis	Control
Nationality		
Saudi	63(65.6%)	24(70.6%)
Yemeni	14(14.6%)	4(11.8%)
Egyptian	9(9.4%)	3(8.8%)
Sudanese	7(7.3%)	1(2.9%)
Jordanian	3(3.1%)	2(5.9%)
Total	96	34
Age(y)		
Mean	28.5	24.8
Range	9 - 52	17.40
Sex		
Male	52 (Saudi 31)	
Female	44 (Saudi 32)	

TABLE 2. *Skin-test allergens.*

Screening panel

	Species	Concentration
Fungi	*Alternaria alternata*	1:20 w/v
	Cladosporium herbarum	1:20
	Rhizopus nigricans	1:20
Pollen	Mixed grasses	
	Acacia	1:40
	Chenopodium album	1:100
Domestic	Cockroach	1:20
	Cat SQ	10 HEP*
	Dog SQ	10 HEP
	Dermatophagoides farinae SQ	10 HEP

Additional allergens in full panel

	Species	Common name	Concentration
Fungi	*Phoma herbarum*		1:20
	Ulocladium chartarum		1:20
	Aspergillus fumigatus		1:20
	Aspergillus niger		1:20
Pollen	*Ambrosia artemisia*	Ragweed	1:100
	Rumex crispus	Dock	1:100
	Triticum sativum	Wheat	1:100
	Salix caprea	Willow	1:100
	Hordeum sativum	Barley	1:100
	Phragmites communis	Reed	1:100
	Brassica napus	Mustard	1:100
	Zea mays	Corn	1:100
	Uttica dioeca	Nettle	1:100
	Carpinus betula	Horbeam	1:100
	Cynodon dactylon	Bermuda grass	1:20
	Corylus avellana	Hazelnut	SQ 10 HEP
	Poa pratensis	Rapgrass	SQ 10 HEP
	Lolium perenne	Ryegrass	SQ 10 HEP
	Phleum pratensis	Timothy grass	SQ 10 HEP
Others	Horse epithelium		SQ 10 HEP
	Dust mite mix		SQ 10 HEP

*HEP indicates in vivo histamine-related standard.

versity Hospital, Riyadh, and were referred for skin-testing. Where possible, consecutive patients were studied, and selection was restricted to nationals of Saudi Arabia or adjacent Middle Eastern countries. A group of 34 patients referred to the ENT clinic with diagnoses excluding rhinitis was skin-tested as a control group. Patient characteristics are summarized in Table 1.

Materials for skin-testing were selected as representing the most common regional allergens from preliminary data from the Riyadh aerobiological study[2] and the fungal allergen and dust study[1] and were supplied by ALK Laboratories, Copenhagen, Denmark, using standardized special purity (SQ) material where possible. A small number of samples were also purchased from Greer Laboratories, USA. As all material was imported, it was not possible, in many instances, to include the precise species growing in the Riyadh area, so representatives of related botanical families had to be included as substitutes.

A screening panel of 11 of the most common allergens was developed and used to test all 96 allergic rhinitis patients and the control group. Twenty-five of the patients found to have clear atopy with this initial screening panel were then recalled for further testing with an extended panel including an additional 21 allergens detected from the above studies. Details of both screening and expanded panel are presented in Table 2.

A standard skin-prick test was used. Droplets of test material were spaced on the forearms at 1- to 2-cm intervals. A positive control with histamine dihydrochloride (1 mg/mL) and a negative control were included for every patient. The skin was punctured through the droplet with a fine blood lancet to lift the upper layer of the dermis. Reactions were read at 10 to 15 minutes, and the mean wheal diameter was recorded. A positive reaction was determined as a minimum wheal diameter of 2.5 mm or more greater than the negative control.[4]

Results

Approximately two thirds of all patients diag-

TABLE 3. *Reactions to individual allergens of screening panel.*

	Total patients			Saudi patients		
Allergen	No. of positive reactions	% of all patients	% of skin-test-positive patients	No. of positive reactions	% of all patients	% of skin-test-positive patients
Chenopodia	31	32.3	54.4	22	34.9	53.6
Cat	28	29.2	49.1	19	30.2	46.7
Grasses	27	28.1	48.8	23	36.5	56.1
Cockroach	18	18.7	31.6	14	22.2	34.1
Dog	15	15.6	26.3	11	17.5	26.8
Dust mite	14	14.6	24.6	9	14.3	22.0
Plantain	9	9.4	15.8	5	7.9	12.2
Cladosporium	3	3.1	5.3	3	4.8	7.3
Acacia	3	3.1	5.3	3	4.8	7.3
Rhizopus	2	2.1	3.5	1	1.6	2.4
Alternaria	1	1.0	1.7	0		

nosed clinically with allergic rhinitis showed one or more positive skin reactions with the screening panel (Table 3). Sixty-three percent of the skin-test-positive patients reacted to two or more allergens. One quarter of the control patients showed a positive skin test.

Sixty-five percent of Saudis and half of the non-Saudis reacted to at least one allergen, and two thirds of these positive subjects reacted to two or more allergens. Positive wheal diameters ranged from 2.5 to 13 mm, with many smaller wheals being excluded by the definition of positivity. Only five of the 129 positive reactions in the allergic rhinitis patients were measured at the lowest 2.5-mm level larger than the negative control (3.9%), and in each instance, the patient also exhibited a wheal of 3 mm or more to another allergen.

Histamine-positive wheals averaged 5.83 ± 1.46 mm for the 57 skin-test-positive patients and 5.57 ± 1.32 mm for the 39 skin-test-negative rhinitis patients. The skin-test-negative control subjects showed a histamine wheal size averaging 4.68 ± 1.40 mm, a significantly smaller response than the rhinitis patients ($P < 0.001$).

The frequency of positive reactions to the individual screening panel antigens is presented in Table 3. *Chenopodium album*, fat hen (representative of the group which includes salt bushes), a panel of mixed grasses, and cat each induced positive reactions in over 25% of all patients tested and in half of the skin-test-reactive patients. For most allergens, the majority of patients showed a wheal size measuring 5 mm or less, but grasses and cat extract induced more than 65% of patients to react with wheals greater than 5-mm diameter.

No significant differences were found in the frequency of positive reactions between males and females. There was a trend for skin-test positivity to be more common in younger patients, with 71% of the 14 patients less than 20 years old reacting positively, 64% of the 39 patients 20 through 29 years old, and 50% of the 42 patients aged 30 and over.

Considering allergens as indoor (cat, dog, cockroach, and dust mite) or outdoor (others), 11 of the 57 skin-test subjects (19%) reacted to the inside battery alone, 27 patients (47%) responded to both inside and outside allergens, and 19 patients (33%) to outside allergens only. Thirty-eight patients (66.7%) reacted to inside allergens, more than half of these to two or more allergens.

To select a minimal panel of skin-test allergens which identified all atopic patients, the frequency of positive reactions to each allergen was compared with the others. Although many patients reacted to two or more allergens, only one is necessary to identify their atopic status. Table 4 lists in rank order the smallest panel which identified all atopic patients and the cumulative effect of adding to the panel.

The extended skin-test panel in the 25 selected atopic patients identified some clinically important additional allergens not included in the original seven (Table 5). Bermuda grass, although represented in the screening grass mix, evoked positive reactions in 22 of the atopic subjects including seven previously negative or positive with wheals less than 2.5 mm above control with the grass mix screen. *Artemisia vulgaris*, *Phragmites communis*, *Zea mays*, and *Salix* were each positive in at least four of the atopics. *Lolium*, *Phleum*, *Poa*, and *Hordeum* are all grasses and were previously detected with grass mix. Individuals of the atopic group reacted to between two and 18 allergens (mean 5 to 7).

TABLE 4. *Rank order of skin-test reactivity.*

	No. of patients	No reaction to allergens	Cumulative positive No. (%)
Chenopodia	31	–	31(54.4)
Cat	28	15	46(80.7)
Grasses mix	27	8	54(94.7)
Cockroach	18	2	56(98.2)
Dust mite	15	1	57(100.0)

TABLE 5. *Positive skin reactions in atopic patients to allergens in expanded test panel.*

Allergen	Common name	No. positive(%)
Cynodon dactylon	Bermuda grass	22(88)
	Cat	14(56)
Chenopodium album	Fat hen	11(44)
Artemisia vulgaris	Mugwort	9(36)
Phragmites communis	Reed	8(32)
Periplaneta americana	American cockroach	7(28)
	Dog	7(28)
Acacia	Trees and shrubs	7(28)
Poa pratenses	Grass	6(24)
Dermatophagoides farina	Dust mite	5(20)
Cladosporium herbarum		5(20)
Phleum pratense	Grass	5(20)
Plantago lanceolata	Plantain	5(20)
Lolium perenne	Grass	4(16)
Zea mays	Maize	4(16)
Salix caprea	Willow	4(16)
Carpinus betula	Hornbeam	4(16)
Hordeum sativum	Grass	3(12)
Ambrosia artemisia	Ragweed	2(8)
Phoma herbarum		2(8)
Ulocladium chartarum		1(4)

Discussion

The study differs from other reports of skin-test results in Saudi patients[5] by selecting allergens for test on the basis of their proved presence in the Riyadh region using aerobiological and ELISA techniques.[1-3] Few patients have never left the region, thereby developing local sensitivities only, but a Riyadh test panel (and later appropriate panels for other regions) would at least present the best opportunity to identify allergens likely to precipitate clinical reactions in rhinitis and asthma within the region.

Three principal conclusions derive from this study. First, atopy among Saudi nationals is common and demands a formal study of incidence to compare with population in other countries. Second, a definitive pattern of sensitivities emerges which is influenced strongly by imported flora. Third, a preliminary allergen screen has been developed for use in Saudi nationals to identify atopy.

The determination of atopy requires a clinical picture of rhinitis, asthma, or eczema, together with a positive skin test and usually a positive family history. Sixty-five percent of Saudi patients diagnosed clinically as having allergic rhinitis showed positive reactions to at least one allergen. This allergen reaction frequency is comparable to values reported from other countries. Eriksson[6] reported 113 of 154 Swedish patients (73.4%) with seasonal rhinitis had positive skin tests. Freidhoff et al,[7] in 262 patients reporting allergies in Baltimore, identified 55% with positive skin reactions, while Tan and Teoh,[8] studying 138 patients with asthma in Singapore, found 69% gave positive skin-test reactions.

As the screening and enlarged test panel had to rely on skin-test material manufactured in Denmark and the United States, many test samples represented family members, but not identical species of flora growing in Saudi Arabia. Species of *Artemisia*, *Ambrosia*, *Rumex*, and *Salix* grow in the Kingdom, but no local species were available for testing. Cross-reactivity between allergens within botanical families is common,[9] but not universal, so the results obtained in this study are likely to represent an underestimate of the true-positive response rate. It is possible that a test panel selected specifically with species growing in the local area might give significantly higher responses.

Both local and imported flora were responsible for positive skin test reactions. The most common response was to grass mix which, on the expanded panel, appeared overwhelmingly to be Bermuda grass, which grows extensively in the Kingdom. While most grass species share many allergens, Bermuda grass has a much more limited allergenic overlap[10] and should be included for its own identity in any further test panel. Clearly, the influence of local irrigation and planting will influence the levels of pollen produced.

Fat hen and salt bush of the Chenopodiaceae family are representative of the group producing the highest pollen level in Riyadh.[2] Not surprisingly, this allergen group commonly provokes reactions in the local population. *Artemisia vulgaris* (mugwort) was included in the expanded panel, as it is a very potent allergen, and species of the genus *Artemisia* (e.g., *A. scoparia* and *A. monosperma*) are widespread in the desert outside Riyadh. The significant number of positive reactions to this in the atopic population (36%) means *Artemisia* should always be included in any local allergy test panel.

Fungal spores are common in Riyadh atmosphere,[1] but the proportion of patients reacting positively to the skin-test material was low. However, *Cladosporium*, *Alternaria*, *Phoma*, *Rhizopus*, and the rarely described *Ulocladium* have each stimulated reactions in some patients and so should be studied further in this environment.

Cat sensitivity was surprisingly common, with over half the atopic Saudis showing positive reactions. As cat-keeping is uncommon in Saudi families, this sensitivity was at first difficult to understand. The SQ material used is standardized with particular care to WHO standards. Contamination is most unlikely. But detailed questioning of positively reacting patients revealed the common presence of wild cats in their environments, in gardens, on stored carpets, and even in open areas of their houses. Clearly the potent allergenic nature of cat dander, with its propensity to cascade, and cat saliva provides a serious contribution to inhalant allergens in the Kingdom.

Immunologic analysis of allergens is a new procedure but a powerful tool in the search for potential allergens.[11] Preliminary information using an ELISA test to detect cockroach antigen revealed a very high level of this material in many household dust samples from the Riyadh region (R. Thorogood, MIBiol, personal communication). Cockroach is increasingly recognized as a very potent allergen,[12] so its presence demands inclusion in any skin-test panel. Eighteen of the 57 atopic patients reacted to American cockroach in the screening series. It is not yet clear if this figure might be much higher if a local species were used for skin-testing.

The house dust mite *Dermatophagoides* (of the species *farinae* or *pteronyssinus*) is ubiquitous in the United Kingdom, the United States, Scandinavia, and many other countries. It depends for its growth on a relative humidity about 50%, rarely the situation in Riyadh with its persistent dry climate of 20% humidity. Neither microscopic nor ELISA analysis has shown significant dust mite concentrations in Riyadh dust samples (R. Thorogood, MIBiol, personal communication). The relatively low dust mite positivity at 25% of the 57 skin-test-positive patients compares with figures as high as 80% for asthmatic children in an environment such as New Zealand (J.D. Wilson, FRACP,PhD, personal communication). The absence of house dust mites in Riyadh indicates that patients with positive reactions to the mite have acquired sensitivity in other centers, either in Saudi Arabia or other countries.

Sorensen et al[5] studied a group of 100 patients with perennial rhinitis in Saudi Arabia and showed Bermuda grass was the commonest allergen, reacting with 33% of all patients tested, while reed, cat, and dust mite were positive in about 15%. They did not include cockroach.

Although a large number of allergens can precipitate allergic rhinitis or bronchial asthma in susceptible patients, the great majority of allergic reactions arise from sensitivity to a very small number of allergens only. Pantin and Merritt[13] showed 95% of patients in the UK with IgE-mediated sensitivities reacted with one or more of a screening pool of only three allergens (grass, mite, and cat). Herbert et al[14] found 90% of atopic asthmatics could be detected with positive skin reactions to four allergens. While this screening group of allergens is insufficient to identify all the potentially triggering material for an individual patient, it does serve as a valuable first step in indicating which patients have an atopic constitution and should be studied in depth. The present study identified a minimum battery of five allergens (Table 4), Chenopodiaceae, Bermuda grass, cat, cockroach, and dust mite, which detected all skin-test-positive patients and would serve as an atopy screen in the Riyadh region. From the expanded panel study, it is likely that *Artemisia* and *Phragmites* might detect some patients unresponsive to other antigens.

While the allergen panel for Riyadh is not complete until local species of potentially allergenic flora are tested, the study indicates that a screening test panel for inhalant allergens in the Riyadh region should include the pollens of *Artemisia*, Chenopodiaceae, Bermuda grass, *Acacia* species, plantain, *Phragmites communis* (reed); the fungi *Cladosporium*, *Rhizopus*, *Ulocladium*, and *Alternaria*; and the domestic allergens cat, cockroach, and dog. This panel might be extended on later investigation. Goat, camel, and sheep should be included where exposure to these species is likely, and rodent sensitivity is currently being investigated.

The authors are extending this work to both Jeddah and the Al-Khobar/Dhahran regions. In each area, the skin-test panel will be devised by studying information from the aerobiological and immunological analysis of the local environment. It is only by this means that an appropriate skin-test panel can be identified for particular regions.

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References

1. Al-Frayh AR, Hasnain SM, Wilson JD, Harfi H. Fungal allergens in the atmosphere of Riyadh: a preliminary communication. Ann Saudi Med 1988;8(4):248-51.
2. Al-Frayh AR, Reilly H, Harfi H, et al. A 12-month aerobiological survey of pollen in Riyadh. Ann Saudi Med (in press).
3. Hasnain SM, Al-Frayh AR, Harfi H, et al. Fungal allergens in the atmosphere of Riyadh: seasonal periodicities. Ann Saudi Med 1989;9(4):000-000.
4. Dreborg S, Belin L, Eriksson NE, et al. Results of biological standardization with standardized allergen preparations. Allergy 1987;42(2):109-16.
5. Sorensen H, Ashoor AA, Maglad S. Perennial rhinitis in Saudi Arabia: a prospective study. Ann Allergy 1986;56(1):70-80.
6. Eriksson NE. Allergy screening in asthma and allergic rhinitis: which allergens should be used? Allergy 1987;42(3):189-95.
7. Freidhoff LR, Meyers DA, Bias WB, et al. A genetic-epidemiologic study of human immune responsiveness to allergens in an industrial population: I. Epidemiology of reported allergy and skin test positivity. Am J Med Genet 1981;9(4):323-40.
8. Tan WC, Teoh PC. An analysis of skin prick test reactions in asthmatics in Singapore. Ann Allergy 1979;43(1):44-6.
9. Martin BG, Mansfield LE, Nelson HS. Cross-allergenicity among the grasses. Ann Allergy 1985;54(2):99-104.
10. Schumacher MJ, Grabowski J, Wagner CM. Anti-Bermuda grass RAST binding is minimally inhibited by pollen extracts from the other grasses. Ann Allergy 1985;55(4):584-7.
11. Lind P, Norman PJ, Newton M, et al. The prevalence of indoor allergens in the Baltimore area: house dust-mite and animal-dander antigens measured by immunochemical techniques. J Allergy Clin Immunol 1987;80:541-7.
12. Hulett AC, Dockhorn RJ. House dust mite (D. farinae) and cockroach allergy in a midwestern population. Ann Allergy 1979;42(3):160-5.
13. Pantin CF, Merrett TG. Allergy screening using a microcomputer. Br Med J 1982;285(6340):483-7.
14. Herbert FA, Weimer N, Salkie ML. RAST and skin test screening in the investigation of asthma. Ann Allergy 1982;49(6):311-4.

SEASONAL PERIODICITIES OF FUNGAL ALLERGENS IN THE ATMOSPHERE OF RIYADH

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أجريت دراسات جوية حيوية لتقويم الأبواغ الفطرية المؤرجة في جو الرياض باستخدام اساليب «بوركارد» للتسجيل بالمقياس الحجمي لمدة ٧ أيام بطريقة مصيدة الأبواغ وأسلوب صفيحة الزرع، وذلك من شهر نوفمبر/تشرين الثاني ١٩٨٦م لغاية أكتوبر/تشرين الأول ١٩٨٧م، تم تسجيل اثنتين وثلاثين فئة جنيسة وشكلية. وكانت غالبية هذه الأبواغ الفطرية تنتمي إلى أبواغ الهواء الجاف للفطريات الغبيرية التي تنشأ من النفايات، وصناديق القمامة، والفاكهة والخضر المخزونة، وماشابه ذلك. وقد شكلت الطوقيات البوغية ما متوسط نسبته ٢٤٫٨٪ من مجموع الأبواغ الهوائية على مدار الشهور الاثني عشر وتروواحت شهريًا بين ٥٫٨٪ و ٤٠٪. كما بلغت نسبة كلّ من السخام (فطر عش الغراب وأنواع أخرى) ١٣٫٤٪ (تراوحت بين ١٫٦٪ و ٢٥٫٦٪)، والفطور من نوع Alternaria ٥٫٦٪ (تراوحت بين ١٫٩٪ و ٩٫٦٪)، والفطور من نوع Uloccladium ٣٫٤٪ (تراوحت بين ١٫٠٪ و ٦٫٨٪) ومن نوع كلّ من Drechslera و Helminthosporium ١٫٨٪ (تراوحت بين ٠٫٧٪ و ٤٫٢٪). أما الأبواغ القاعدية فقد شكّلت نسبتها ٣٫١٪ (تراوحت بين ١٫٥٪ و ٥٫٧٪) وتم تسجيل نسب التركيز الساعية (في الساعة) لجميع هذه الفئات وشكلت الطوقيات البوغية أعلى نسبة بينها. كما أظهرت الدوريات الموسمية زيادة في نسبة التركيز خلال الأشهر الدافئة وانخفاضا في فصل الشتاء.

Aerobiological studies to evaluate allergenic fungal spores in the atmosphere of Riyadh were conducted using Burkard volumetric 7-day recording spore trap and culture plate techniques from November 1986 through October 1987. Thirty-two generic and morphologic categories were recorded. The majority of these fungal spores belonged to dry-air spora of conidial fungi, originating from garbage, rubbish bins, stored fruits and vegetables, and the like. *Cladosporium* spp. constituted 24.8% (mean value) of total air spora over the 12-month period, ranging monthly from 8.5% to 40%; smuts (*Ustilago* and other species) 13.4% (range, 1.6% to 25.6%); *Alternaria* spp. 5.6% (range, 1.9% to 9.6%); *Ulocladium* spp. 3.4% (range, 1.0% to 6.8%); *Chaetomium* 1.8% (range, 0.7% to 4.2%); *Drechslera* and *Helminthosporium* 1.8% (range, 0 to 5.4%). Basidiospores constituted 3.1% (range, 1.5% to 5.7%). Peak hourly concentrations for all categories were recorded, *Cladosporium* having the highest concentration. Seasonal periodicities showed an increase in concentration in the warmer months and a decline in the winter.

The role of some fungal spores and pollen grains present in the air is well known in the etiology of respiratory allergic diseases such as asthma and allergic rhinitis. Before symptoms and exposure to such allergens can be related, however, information on the qualitative nature and distribution patterns is required.

In a previous communication[1] we described the airborne fungal allergens identified in the atmos-

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phere of Riyadh, using both viable and visual methods of trapping. This article describes the nature and distribution of airborne fungal spores based on 12 months of aerobiological studies in Riyadh from November 1986 through October 1987.

Methods

The Burkard volumetric 7-day recording spore trap and gravity culture plate technique with general purpose culture media were used to analyze the air spora. A detailed description of both techniques has already been presented in our preliminary communication.[1]

The Burkard volumetric spore trap was operated on the flat roof of the clinical building of King Faisal Specialist Hospital and Research Centre (KFSH&RC) about 6 meters above ground level. The site is approximately 3 km from the main city center with clinical buildings of equal height in the east and northeast, shaded parking area in the south, and a large garden and parkland area in the west. The compound is surrounded by various indigenous and imported plant species. The whole area is irrigated abundantly each day.

The trap operates on the principle of "impaction through suction" with 2-mm movement of the drum each hour. A suction rate of 10 liters per minute was maintained. Tapes were mounted with gelvatol-phenol mixture. Spores were counted in 60 fields per 24-hour period beginning from 1 AM which involved handling of three slides for each day's count. Spores were converted to cubic meter of air by a factor obtained by applying the following formula: concentration propagules $m^{-3} = N_T \times A_E/n \times a \times V_a$, where N_T is the total number of spores counted in "n" areas (= x); n is the number of field areas counted (= 5 field areas); a is a field area, mm^2 (= 0.15205 mm^2); V_a is the air volume sampled, m^{-3} (= 0.6 m^3); and A_E is the total effective area, mm^2 (i.e., long axis of orifice × distance tape moves in 1 hour, = 14 × 2 = 28 mm^2).

Each alternate hour's counts were added to calculate daily, weekly, and monthly means and, based on the above equation, were converted to spores per cubic meter. Maximum or peak hourly concentrations of various spores per cubic meter of air were determined. Percentages of individual types were calculated against the total spores counted.

Results

A total of 32 different generic and morphologic categories of fungal spores were recorded during the 12-month period. The majority of these spores came from dry-air spora belonging to the dematiacious hypomycetes group of fungi imperfecti and originating from a wide range of sources, both indoors and outdoors, including dead and decaying vegetation, garbage, rubbish bins, stored plants, fruits, and vegetables.

The mean monthly concentrations of total spores ranged from 150 spores per cubic meter in January to 500 spores per cubic meter in May, displaying a seasonal trend to rise in concentration during warmer months. A decline in spore concentrations was noted in the coldest months.

The genera which were present consistently almost 12 months with higher individual percentages were termed as "major components." These included *Cladosporium*, smuts, *Alternaria*, *Ulocladium*, *Chaetomium*, *Drechslera*, and *Helminthosporium* as well as basidiospores. The distribution of these generic categories is summarized in Table 1. The seasonal distribution is presented in Figure 1. Peak hourly concentrations of some categories are presented in Figure 2.

Major Components

Conidia of several species of *Cladosporium* including *C. herbarum*, *C. cladosporioides*, *C. macrocarpum*, and *C. sphaerospermum* were observed. They constituted 24.8% of all spores during the 12-month period and ranged from 8.5% in June to 40% in December (39.4% in March). Peak hourly concentrations of *Cladosporium* exceeded 6000 spores per cubic meter in March.

Smuts, a common name for Ustilaginales fungi, responsible for many phytopathogenic diseases in crop plants, constituted 13.4% of the total spores during the year. This group also included *Tilletia caries* and *Sphacelotheca*-type smut chalamydospores, the commonest one being *Ustilago nuda* (on wheat). The seasonal maximum concentrations was recorded in May. Peak hourly concentrations of smuts reached 976 spores per cubic meter in April.

TABLE 1. *Percentage of the major spore types in the total air spora, based on each month's catch using Burkard volumetric spore trap.*

Month	*Cladosporium*	Smuts	*Alternaria*	*Ulocladium*	*Drechslera* and *Helminthosporium*	*Chaetomium*	Basidiospores	Damaged spores	Others (minor components)	Total
Nov 86	33.8	9.2	4.4	1.0	1.3	3.1	2.0	18.7	26.5	100
Dec 86	40.0	1.6	6.0	2.8	0.7	3.0	2.5	22.7	20.7	100
Jan 87	12.5	11.4	6.4	4.5	2.3	4.2	2.3	24.2	32.2	100
Feb 87	27.6	6.2	6.6	3.6	1.3	1.6	4.9	19.4	28.8	100
Mar 87	39.4	9.5	7.8	6.8	0.4	1.4	4.2	9.3	21.2	100
Apr 87	14.0	12.0	9.6	6.2	1.8	1.6	3.7	27.0	24.1	100
May 87	9.2	25.6	7.4	4.0	1.4	1.3	2.6	35.0	13.5	100
Jun 87	8.5	23.5	3.8	4.0	0.2	0.8	2.0	53.0	4.2	100
Jul 87	37.0	24.0	1.9	1.4	0.3	1.1	3.3	22.2	8.8	100
Aug 87	26.2	17.2	5.1	2.3	1.8	0.7	1.5	33.4	11.8	100
Sep 87	23.5	14.8	2.2	2.4	5.4	1.1	5.7	29.3	15.6	100
Oct 87	24.8	6.0	5.2	2.0	5.4	2.2	3.0	33.9	17.5	100
Total % score	296.5	161.0	66.4	41.0	22.3	22.1	37.7	328.1	224.9	1200
Mean % for whole year	24.8	13.4	5.6	3.4	1.8	1.9	3.1	27.3	18.7	100

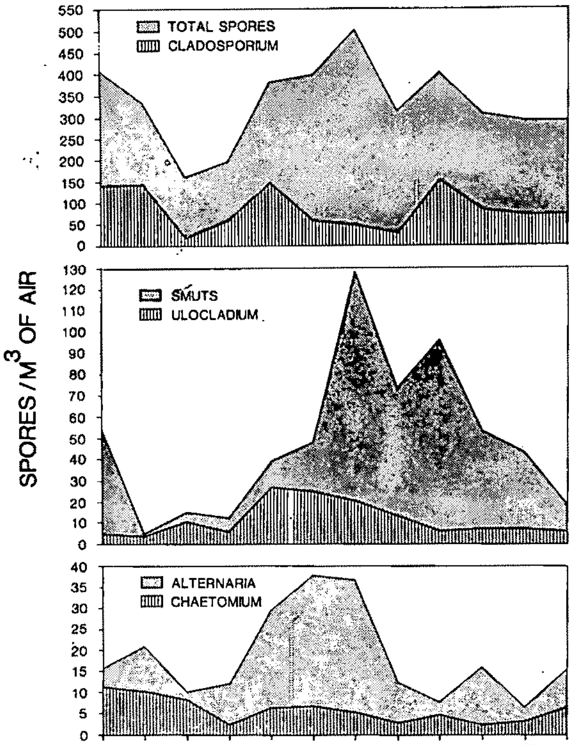

FIGURE 1. Seasonal periodicities of major components of Riyadh atmosphere (KFSH&RC site), November 1986 through October 1987. (Concentration scales of spores per cubic meter of air are different.)

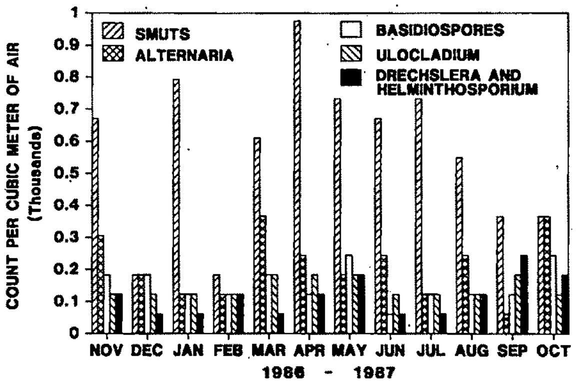

FIGURE 2. Peak hourly concentration levels per cubic meter of air of some spore categories, recorded using Burkard volumetric spore trap from November 1986 through October 1987.

Ulocladium, a rarely reported genus from the air, sometimes mistaken as *Alternaria*, was encountered throughout the period. *Ulocladium* constituted 3.4% of all spores during the year and ranged from 1.0% in November to 6.8% in March. The peak hourly concentration of *Ulocladium* was 183 spores per cubic meter recorded in March, April, May, and September. In April and September, the value was recorded several times.

Species of *Alternaria*, a defined allergenic genus in the United States, were present in all months.

Mean monthly concentration was about 40 spores per cubic meter in April and May. *Alternaria* constituted 5.6% for the year and ranged from 1.9% in July to 9.6% in April. The peak hourly concentration was recorded as 366 spores per cubic meter in March and October.

Drechslera and *Helminthosporium*, two different genera but somewhat similar in their conidial morphology, were grouped together. They constituted 1.8% for the year and ranged from 0.4% in March to 5.4% in September and October. The peak hourly concentration reached 244 spores per cubic meter in September.

Chaetomium is an ascomycetous fungus, and ascospores (spores) were recorded in all 12 months. *Chaetomium* constituted 1.8% for the year and ranged from 0.7% in August to 4.2% in January. Peak hourly concentration of *Chaetomium* reached 183 spores per cubic meter.

Basidiospores, the majority of which are constituents of damp and wet environments, were also recorded. They were mainly colored, except on rare occasions when hyaline basidiospores were encountered. Basidiospores of *Merulius lacrymans* (an allergenic species), *Gymnopilus, Coprinus*, and *Hypholoma* types were noted. This group constituted 3.1% during the 12-month period and ranged from 1.5% in August to 4.9% in February and 5.7% in September. The peak hourly concentration reached 244 spores per cubic meter both in May and October. A lesser concentration of these spores ranging from 122 to 243 per cubic meter was recorded throughout the year, except in June when maximum recording was 61 spores per cubic meter.

Minor Components

Spore categories showing sporadic occurrence with mean monthly concentrations up to 100 per cubic meter were termed "minor components" (Table 2). These included *Arthrinium, Asperisporium, Curvularia, Epicoccum, Nigrospora,*

TABLE 2. *Seasonal periodicities of minor components of the air spora which displayed sporadic appearance.**

	1986		1987									
	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct
Conidial group												
Arthrinium	+	0	+	0	+	+	+	0	0	0	0	0
Asperisporium	+	+	0	0	+	+	0	0	0	0	0	+
Botrytis†	0	0	0	+	0	0	0	0	0	0	0	0
Curvularia†	0	+	+	0	0	0	0	0	0	0	0	+
Epicoccum†	+	+	+	0	+	0	0	0	0	0	0	+
Nigrospora†	+	+	+	+	+	+	+	+	0	+	+	+
Periconia	0	+	0	+	+	+	+	+	+	0	+	0
Pithomyces	+	0	0	0	0	+	+	0	+	0	+	0
Stemphylium†	0	+	0	+	+	+	+	0	0	+	+	+
Trichothecium†	0	0	0	0	0	0	+	0	0	0	0	+
Torula†	+	+	+	+	+	+	+	+	+	+	0	+
Spores‡ < 10 μm	++++	++	++	+++	++	+++	+	+	+	++	++	++
Basidiospore group												
Ganoderma†	0	0	0	0	0	0	0	0	0	0	0	+
Rust spores† (uredospores)	0	+	0	+	+	+	0	0	0	0	0	0
Ascospore group												
Ascospores, 3 septate	+	+	+	+	0	+	0	0	+	+	0	0
Ascospores, nonseptate	+	+	+	+	+	+	+	0	0	0	0	+
Leptosphaeria	0	0	0	0	0	0	+	+	0	0	0	+
Leptosphaerulina	0	+	0	0	0	0	0	0	0	0	0	0
Pleospora	+	+	0	0	0	+	0	0	+	0	+	0
Sporormiella	0	+	0	+	+	+	0	+	0	+	0	0
Venturia	+	0	+	+	+	+	+	0	+	0	0	+
Xylaria†*-Hypoxylon*	+	0	0	0	0	0	0	0	0	0	0	0
Miscellaneous group												
Hyphal fragments	+++	+++	+++	++	+++	+++	++++	+++	+++	+++	+++	+++
Algae	0	0	0	0	0	0	+	0	0	+	0	0

*Frequency or occurrence is based on mean monthly concentration per cubic meter of air where + = 1-5; ++ = 6-25; +++ = 26-50; ++++ = 51-100 spores.

†Allergenic genera.

‡Includes *Aspergillus, Penicillium*, and other indistinguishable spores, mainly hyaline and greenish, having a size < 10 μm in diameter.

Periconia, Pithomyces (facial eczema spores), *Stemphylium, Trichothecium, Torula, Leptosphaeria, Pleospora, Sporormiella,* and *Venturia,* and other sporadic categories.

Spores from two important contaminating genera, *Aspergillus* and *Penicillium*, obscured by the dust deposit, were grouped under spores $< 10\ \mu m$ along with other hyaline conidia.

Sharp fluctuations in hourly and daily values of many genera were recorded. For example, on 24 April, the mean daily concentration of total spores recorded was 269 spores per cubic meter. On 25 April, the level rose to 772 spores per cubic meter, coming down almost to the previous peak of 290 spores per cubic meter on 26 April. Similarly, *Cladosporium* mean daily value on 28 March was 39 spores per cubic meter, rising to 900 spores per cubic meter on 29 March. *Alternaria*, which showed a concentration of 86 spores per cubic meter on 25 April, declined to 25 spores per cubic meter on 26 April. Sharp fluctuations were also noted in other genera. Changes in daily concentrations are usually dictated by the sharp hourly changes in spore levels and are attributable to changes in meterologic factors such as wind direction.

On 25 April, a variety of spores were recorded with the highest mean daily concentration. Thus, it was the most polluted day among the days slides were scanned.

Discussion

The present study is part of a comprehensive aerobiological survey of fungal spores in the Saudi environment. The study revealed that, in spite of low natural humidity ($< 40\%$), a large number of fungal genera of class Deuteromycotina (fungi imperfecti), mostly of dry nature, originating from common sources such as garbage and rubbish bins, are present in the atmosphere of Riyadh. The majority of allergenic spores identified worldwide to date belong to the same class of fungi.[2]

The mean monthly concentration (which absorbs the peaks) of various genera ranged from 150 to 500 spores per cubic meter, and the maximum concentration for only one category, *Cladosporium*, for 1 hour exceeded 6039 spores per cubic meter. Clinical experience in the West has demonstrated that the abundance of environmental fungal agents represents sufficient exposure for a large number of individuals to become sensitized.[3]

There has been no systematic study on the threshold of fungal spores capable of inducing symptoms in susceptible individuals. The value determined on the basis of relative cases differs among workers.[4,5] Threshold figures based on tenuous extrapolations from gravity slide data (which are nonvolumetric) in many cases appeared to underestimate true threshold exposure requirements.[6] However, once sensitization has taken place in sensitive individuals, as a result of massive exposure, even for a shorter period, a much smaller concentration of spores may induce symptoms.[7] It can be expected that the mean monthly concentration of any generic category presented, together with the maximum value (usually several times higher), may cause an allergic attack in sensitized individuals.

Seasonal periodicities of major components based on mean monthly values as presented exhibit a tendency to rise and peak in the summer season. Three peaks in *Cladosporium* may relate to the availability of various growth sources in the area. This genus has more than 30 species growing on over 100 different substrates. Species of *Drechslera* (and *Helminthosporium*) may be thermotolerant (thriving above 40°C). *Chaetomium*, on the other hand, is an ascomycetous fungus, which generally prefers high moisture content with low temperature. Basidiospore periodicity remains unexplained. Although there is no well-defined season for fungi,[8] as the number of spores and pollen counted are influenced by the sampling technique, locality, surroundings, height above ground level, meterologic factors, and irrigation, as well as spore discharge rhythm (active or passive), both seasonal distribution and circadian pattern for one type or more may vary.

In Riyadh the growth opportunities are greater for conidial fungi than for basidiomycetous ones; irrigation and surroundings of the present site offer a "microclimatic" situation, evident by the year-round presence of both basidiospores and ascospores. This indicates that growth sources of many different genera are present with the availability of artificial humidity. As the spore clouds dilute from the source area, a regional quantitative variation is expected to emerge when the data from two other sites, currently under investigation in the city, are ready for comparison.

Clinical experience indicates that many patients react weakly or negatively in skin-prick testing with commercial fungal extracts, and the information on allergenicity to an allergen or allergens is usually based on the result of such tests rather than on the direct relationship between the occurrence in the environment of the organism concerned and the onset of symptoms in the allergic patient.[9] Certain problems are associated with the preparation of a reliable fungal extract[8,10] from an appropriate species or strain, and the potency of any prepared extracts varies from company to company or from batch to batch.[11] Even within the testing procedure itself, there appears to be a significant variation. In a comparative study of scratch, intradermal, and provocation tests,[12] *Alternaria* gave 56% positive reaction in intradermal test compared to 4.5% in scratch test. Similarly, *Cladosporium, Aspergillus, Penicillium*, and *Helminthosporium* gave 39%, 40%, 38%, and 50% positive reactions, respectively, in intradermal tests, compared to 6.6%, 3.6%, 1.3%, and 2.0% in scratch tests. The value for nasal provocation test with the same antigen was also about 10-fold higher than the scratch test. Bruce[13] emphasized that to confirm the bronchial manifestation of allergic individuals, the skin test should be replaced by the bronchial provocation test.

Further, on skin testing with extracts of four different species of *Cladosporium*, atopic persons in the U.S. Midwest showed variable reactivity patterns suggesting allergenic differences among the species.[6] Our studies indicate five or six different species of *Cladosporium* were present throughout the 12-month period. Availability and testing of commercial extract are normally limited to two species only, i.e., *C. herbarum* and *C. cladosporioides*.

Unlike basidiospores and ascospores, which are characteristic of damp and wet climates such as Auckland[14] and New Orleans,[15] presence of dry-nature fungi identified in Riyadh is in agreement with similar surveys in the temperate region. Davies[16] used a similar method (Hirst spore trap) in Kuwait and identified *Cladosporium* and *Ustilago* as two major spores in the Kuwait atmosphere. *Cladosporium* alone constituted 66% of the total fungal spores. This is comparable with our data where *Cladosporium* (up to 40%) and *Ustilago* (up to 13.4%) were the top two spore categories. The only available study of indoor allergens in the Eastern Province[17] using the culture plate method documented *Aspergillus, Cladosporium, Penicillium, Mucor, Alternaria*, and unidentified colonies of 10 or more among a total of 44 cultures, which confirms our findings in both visual and viable identification. We have already documented[1] *Rhizopus, Aspergillus, Penicillium, Alternaria*, and *Cladosporium* through culture plate studies.

Presence of innumerable thick dust particles obscuring the identity of hyaline and smaller spores as well as the efficiency of this trap which varies with wind (air intake in the trap is not equal to the wind speed owing to speed fluctuation) and particle size[18] and further limitation imposed by the height, as the ground level is considered to be more contaminated, the data presented may underestimate the actual concentration to which an individual is exposed.

While the main emphasis in this paper is on outdoor allergens, indoor allergens must not be forgotten. Spores derived from indoor growth can be a source of perennial allergic symptoms. Food storage areas, soiled upholstery, and garbage containers are favored sites for domestic mold growth. Cattle hair and other organic substances (e.g., wool) are readily colonized by fungi. Cellulose splitting organisms may dominate the mycoflora of cotton, kapok, and conventional wallpaper. A number of known allergenic species of fungi including *Aureobasidium, Geotrichum, Rhizopus, Mucor, Aspergillus, Penicillium, Drechslera*, and *Ulocladium*, have already been isolated from homes of asthmatic patients in Riyadh (S.M. Hasnain, personal communication). This emphasizes the importance of some difference in the indoor mycoflora. A possible link of such different indoor fungi and incidence of asthma and perennial allergic rhinitis needs to be investigated thoroughly.

Complexities of pleomorphism (asexual and sexual forms of fungus) and synonism (taxonomical change of name) also need to be clarified. Identification of *Drechslera* spp., which are very similar to *Helminthosporium* spp., resulting in some synonymic changes, requires the selection of an appropriate extract for testing and treatment. The similarity of these two genera has led in the past to the preparation of extract of *Drechslera* labeled as *Helminthosporium*.[19] The same situation arises for many other pleomorphic fungi.

The clinical importance of high levels of some spore categories in outdoor air, especially several different species of *Cladosporium* and *Alternaria*, as well as the ubiquitous presence of the rarely reported genus, *Ulocladium*, from the air, necessitate an extensive in vivo and in vitro investigation of asthmatic patients to confirm the importance of these allergenic spores and that of *Ulocladium* in the respiratory allergic problems in Saudi Arabia.

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References

1. Al-Frayh A, Hasnain SM, Wilson JD, Harfi HA. Fungal allergens in the atmosphere of Riyadh: a preliminary communication. Ann Saudi Med 1988;8(4):248-51.
2. Burge HA. Fungus allergens. Clin Rev Allergy 1985;3(3):319-29.
3. Kjell A, Aukrust L. Immediate hypersensitivity response to fungal agents. In: Al-Doory Y, Domson JF, eds. Mould allergy. Philadelphia: Lea and Febiger, 1984:133-46.
4. Davies RR, Smith LP. Forecasting the start and severity of the hay fever season. Clin Allergy 1973;3:263-7.
5. Frankland AW, Davies RR. Allergie aux spores de moisissures en Angleterre. Poumon Coeur 1965;21:11-31.
6. Solomon WR, Mathews KP. Aerobiology and inhalant allergens. In: Middleton E, Reed CE, Ellis EF, eds. Allergy: principles and practice. 2nd ed. St. Louis: CV Mosby Co, 1983:1143-1202.
7. Hyde HA. Atmospheric pollen and spores in relation to allergy. Clin Allergy 1972;2:153-79.
8. Salvaggio J, Aukrust L. Mold induced asthma. J Allergy Clin Immunol 1981;68(5):327-46.
9. Maunsell K. The seasonal variation of allergic bronchial asthma in relation to the concentration of pollen and fungal spores in the air in 1954, 1955 and 1956. Acta Allergologica 1958;12:257-76.
10. Lehrer SB, Aukrust L, Salvaggio JE. Respiratory allergy induced by fungi. Clin Chest Med 1983;4(1):23-41.
11. Aas K, Leegaard J, Aukrust L, Grimmer O. Immediate type hypersensitivity to common moulds: comparison of different diagnostic materials. Allergy 1980;35(5):443-51.
12. Collins-Williams C, Nizami RM, Lamenza C, et al. Nasal provocative testing with molds in the diagnosis of perennial allergic rhinitis. Ann Allergy 1972;30:557-61.
13. Bruce RA. Bronchial and skin sensitivity in asthma. Int Arch Allergy 1963;22:294-305.
14. Hasnain SM, Wilson JD, Newhook FJ. Fungi and disease: fungal allergy and respiratory disease. NZ Med J 1985;98:342-6.
15. Salvaggio J, Hasselblad V, Seabury J, et al. New Orleans asthma: II. Relationship of climatologic and seasonal factors to outbreak. J Allergy 1970;45:257-65.
16. Davies RR. Spore concentration at Ahmadi, a new town in Kuwait. J Gen Microbiol 1969;55:425-32.
17. Sorensen H, Ashoor AA, Maglad S. Perennial rhinitis in Saudi Arabia: a prospective study. Ann Allergy 1986;56:76-80.
18. Ogden EC, Raynor GS, Hayes JV, et al. Manual for sampling airborne pollens. New York: Hanfer Press, 1974:40-96.
19. Hoffman DR. Mould allergens. In: Al-Doory Y, Domson JF, eds. Mould allergy. Philadelphia: Lea and Feibiger, 1984:104-16.

MORPHOLOGIC AND IMMUNOPATHOLOGIC SPECTRUM OF MALIGNANT LYMPHOMA: REVIEW OF 211 CASES

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روجعت سلسلة مكونة من ٢١١ ورما لمفيا خبيثا لدى بالغين وصنفت وفقا لصيغة العمل الدولية. كانت درجة خمسة من الأورام المصنفة (٤ر٢٪) منخفضة ودرجة ١١٥ (٥ر٥٤٪) متوسطة ودرجة ٨٥ (٣ر٤٠٪) عالية. وباستخدام مجموعة من الأضداد وحيدة النسيلة ضد المستضدات السطحية للخلايا (ت) والخلايا (ب) لتحديد النوع المناعي النسيجي لمئة وستة أورام تبين أن أورام الخلايا (ب) ٥١ (١ر٤٨٪) وأورام الخلايا (ت) ٤١ (٧ر٣٨٪) بينما كانت ١٤ (٢ر١٣٪) من الأورام غير محددة. قورنت هذه النتائج بنتائج عدة دراسات من أقطار أخرى نشرت مؤخرا، وبدت نسبة الأورام اللمفية النشطة في سلسلتنا مرتفعة نسبيا. كما كانت نسبة أورام الخلايا (ت) في دراستنا أعلى بدرجة ملحوظة مما هي في الدراسات الأخرى.

A series of 211 malignant lymphomas in adults were reviewed and classified according to the international working formulation. Of those classified, five (2.4%) were low-grade, 115 (54.5%) intermediate-grade, and 85 (40.3%) high-grade lymphomas. Immunohistologic typing of 106 lymphomas was performed using a panel of monoclonal antibodies against T- and B-cell surface antigens. This revealed 51 (48.1%) B-cell and 41 (38.7%) T-cell lymphomas with 14 (13.2%) indeterminate. These results were compared with those from several recently published studies from other countries. The proportion of aggressive lymphomas in our series appeared to be relatively high. Furthermore, immunohistologic data in our study indicated a significantly higher proportion of T-cell lymphomas as compared to other studies.

Malignant lymphoma is one of the most common malignant neoplasms in Saudi Arabia.[1] A few studies describing various clinical and therapeutic aspects of malignant lymphoma in Saudi Arabia have been previously reported.[2-4] However, to the best of our knowledge, a detailed study outlining the histopathologic and immunohistologic characteristics of malignant lymphoma in this country has not been published.

The purpose of this study was to review the morphologic and immunopathologic features of malignant lymphomas seen in our laboratories and compare our findings with those from recently published studies from centers in other countries.

Materials and Methods

All malignant lymphomas in adults diagnosed histologically between January 1984 and December 1987 were identified. Cases in which the biopsies were performed in other institutions as well as those cases in which the biopsy material was inadequate were excluded. A total of 211 cases were selected in which the biopsy was performed at King Faisal Specialist Hospital and Research Centre and the tissue obtained was adequate for histologic diagnosis.

Tissues were fixed in 10% buffered formaldehyde solution and B-5 solutions, dehydrated in graded alcohols, and embedded in paraffin in a routine manner. Three- to four-micron sections were stained with hematoxylin and eosin. Special stains such as periodic acid-Schiff (PAS) and

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methyl green-pyronine (MGP) were used in selected cases whenever indicated. Imprint smears from the fresh tissues were made and stained by Diff-Quik stain. Appropriate pieces of tissue were snap-frozen for cryostat sections which were used for immunohistologic staining. The sections were stained using avidin-biotic complex technique using a panel of monoclonal antibodies against a variety of T- and B-lymphocyte surface antigens. Immunohistologic staining for phenotyping of malignant lymphoma was carried out in all cases where unfixed fresh tissue was available, and therefore there was no selection of cases.

Slides from all the cases were reviewed by two pathologists (M.A.A. and M.A.). All lymphomas were classified according to the international working formulation.[5] The lymphomas containing large cells (less than five per high-power field) were classified as small cell type. The lymphomas containing 5 to 15 large cells per high-power field were classified as mixed, while those with large cells more than 15 per high-power field were categorized as large cell lymphomas.[6]

Results

Histopathologic classification of the 211 lymphomas according to the working formulation is given in Table 1 (Figures 1-7). Five lymphomas (2.4%) were classified as low grade, 115 (54.5%)

TABLE 1. *Classification of 211 non-Hodgkin's lymphomas using the working formulation.*

Low grade	
Small lymphocytic	3
Follicular small cleaved	2
Follicular mixed	0
Subtotal	5(2.4%)
Intermediate grade	
Follicular large cell	4
Diffuse small cleaved	22
Diffuse mixed	11
Diffuse large cell	78
Subtotal	115(54.5%)
High grade	
Immunoblastic	79
Lymphoblastic lymphoma	3
Small non-cleaved	3
Subtotal	85(40.3%)
Others	6(2.8%)
Total	211(100.0%)

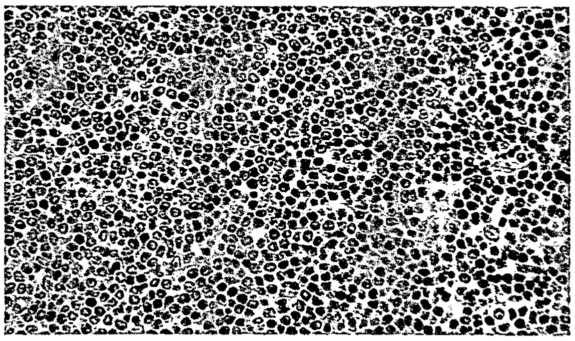

FIGURE 1. Well-differentiated lymphocytic lymphoma (hematoxylin and eosin stain, original magnification, ×150).

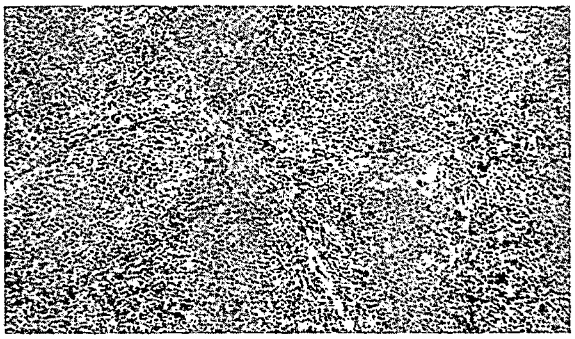

FIGURE 2. Follicular small cleaved lymphoma (hematoxylin and eosin stain, original magnification, ×100).

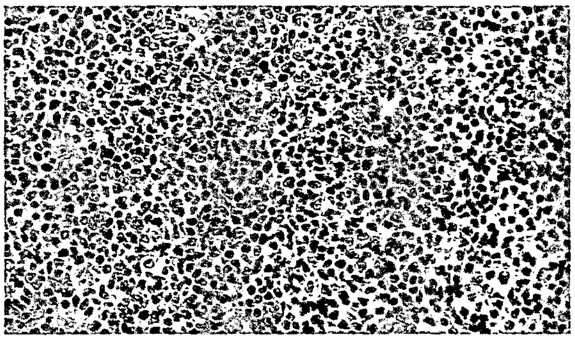

FIGURE 3. Diffuse small cleaved lymphoma (hematoxylin and eosin stain, original magnification, ×150).

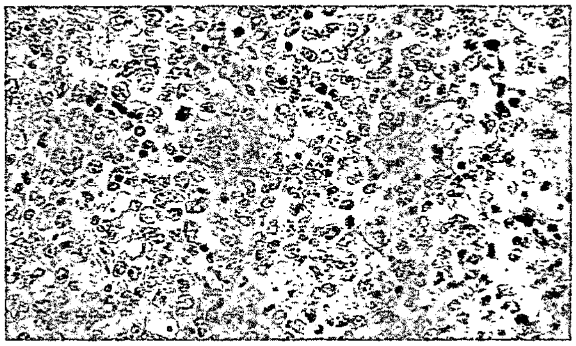

FIGURE 4. Diffuse large cell lymphoma (hematoxylin and eosin stain, original magnification, ×150).

as intermediate grade, and 85 (40.3%) as high grade. Thus, of the 211 malignant lymphomas, 200 (94.8%) were aggressive lymphomas (intermediate or high grade).

Immunophenotyping of the lymphoma was carried out in 106 cases. Of these, 51 (48.1%) were B-cell type, 41 (38.7%) were T-cell type, and 14 (13.2%) could not be classified with certainty. Of the 75 large cell lymphomas, 37 (49.3%) were B-cell type, and 28 (37.3%) were T-cell type, while in 10 cases (13.3%) the results were indeterminate.

Comparison With Recently Published Studies

Our findings from this study were compared with data from recently published studies from several other countries in which a similar classification of malignant lymphoma was used (Table 2).[5,7,8] This comparative evaluation revealed that in our series, low-grade lymphomas were extremely uncommon, representing only 2.4% of the entire group. This is in sharp contrast to the studies from the United States where low-grade lymphomas constitute 18.9% to 34.2% of the total. Another significant difference is in the relative proportion of high-grade lymphomas. These lymphomas constitute 2.6% to 26.3% of the total in studies from the United States. By contrast, in our series, 40.2% of the lymphomas were high grade. This is similar to the figures from East China where 43.2% of the lymphomas were categorized as high grade.

Immunohistologic studies in our series indicated that 37.3% of large cell lymphomas were of T-cell origin. In several previously published studies, the proportion of T-cell lymphoma varied from 3% to 23%.[9-12] In one study, however, T-cell lymphomas represented 42% of the total.[13]

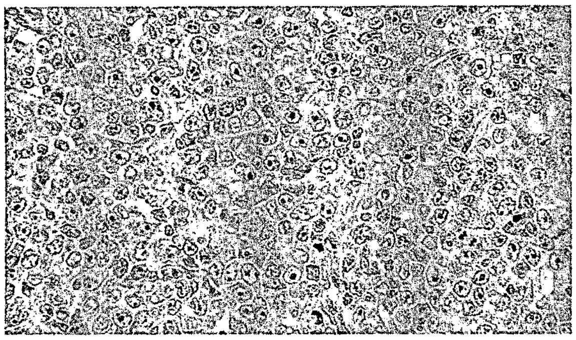

FIGURE 5. Immunoblastic sarcoma (hematoxylin and eosin stain, original magnification, ×150).

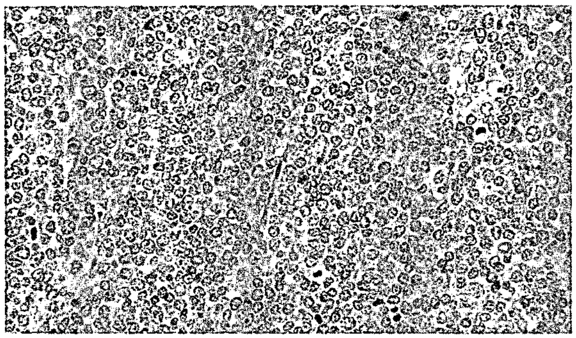

FIGURE 6. Lymphoblastic lymphoma (hematoxylin and eosin stain, original magnification, ×150).

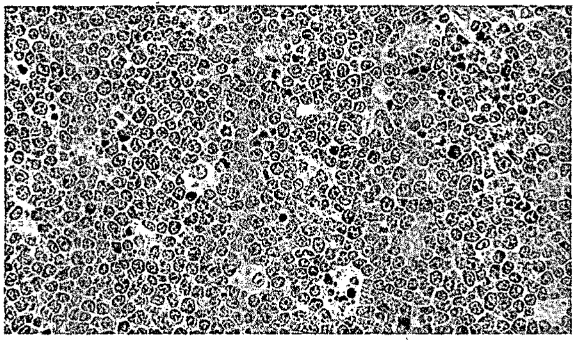

FIGURE 7. Small noncleaved lymphoma (hematoxylin and eosin stain, original magnification, ×150).

TABLE 2. *Comparison of classification of malignant lymphomas using the working formulation.*

	US & Puerto Rico[8] No. (%)	Nebraska[7] No. (%)	East China[7] No. (%)	US[5] No. (%)	Milan, Italy[5] No. (%)	Present study No. (%)
Low grade	4227(34.3)	94(18.9)	24(12.5)	393(49.0)	67(18)	5(2.4)
Intermediate grade	7865(63.9)	269(54.0)	75(39.1)	304(37.9)	194(52)	115(54.5)
High grade	227(1.8)	131(26.3)	83(43.2)	96(12.0)	112(30)	85(40.3)
Others	–	4(0.8)	10(5.2)	9(1.1)	–	6(2.8)
Total	12,319(100)	498(100)	192(100)	802(100)	373(100)	211(100)

Discussion

The results from our study indicate that, compared to studies from the United States, the relative proportion of low-grade lymphomas in our series was considerably lower. The percentage of high-grade lymphomas in our series by contrast was considerably higher. These differences were less striking when our results were compared with data from eastern China and Milan, Italy (Table 3).

TABLE 3. *Immune marker expression in aggressive lymphomas.*

Study	B-cell No. (%)	T-cell No. (%)	Indeterminate No. (%)	Total no.
Pallesen et al[9]	32(60)	12(23)	9(17)	53
Doggett et al[10]	47(54)	12(14)	28(32)	87
Cossman et al[13]	31(53)	25(42)	3(5)	59
Aisenberg et al[11]	15(55)	4(15)	8(30)	27
Rudders et al[12]	10(33)	1(3)	19(64)	30
Present series	37(49)	28(37)	10(13)	75

The reasons for the occurrence of a relatively high proportion of aggressive lymphoma in Saudi Arabia as compared to other countries, most notably the United States, are not clear. One possible explanation may be that the patients in this country tend to seek medical advice at a much later stage when the disease is clinically advanced. Several studies have shown that low-grade lymphomas, such as poorly differentiated lymphocytic lymphomas, may undergo progression into higher-grade lymphomas in a significant proportion of cases.[14,15] Therefore, it is conceivable that if the patients are diagnosed at a later stage during the clinical course, a higher proportion of aggressive lymphomas would be encountered. This would explain some, but probably not all, cases of aggressive lymphoma. Another explanation for these differences may be that the etiology and pathogenesis of malignant lymphoma in Saudi Arabia is different from that in Western countries. Different etiopathogenetic factors could conceivably give rise to lymphomas which vary in morphologic appearance as well as clinical behavior.

The etiology and pathogenesis of malignant lymphoma are poorly understood. There may be a role for such factors as personal hygiene, socioeconomic status, living standards, and exposure to various bacterial, parasitic, and viral infections. In addition, ionizing radiation and a variety of chemicals, such as fertilizers and herbicidal agents, have been implicated.[7,16] In Saudi Arabia, the practice of intermarriage within families may be an additional contributing factor. Conceivably, such marriages could result in an abnormal aggregation of genes which are especially susceptible to development of aggressive lymphoma. Detailed epidemiologic studies are needed in order to understand the etiology and pathogenesis of malignant lymphoma in this country.

Malignant lymphoma represents a major challenge to the medical profession in Saudi Arabia, not only because it is one of the commonest malignancies but also because an overwhelming majority of the lymphomas in this country are aggressive in nature. The aggressive lymphomas are a major group of non-Hodgkin's lymphomas characterized by advanced disease in most cases and a rapidly progressive clinical course. Until recently, the disease was fatal, with most of the patients dying within 1 to 2 years. However, over the last 10 years, use of intermittent high-dose combination chemotherapy has significantly increased the survival time for patients with both local and advanced disease. It is also felt that many of the patients can be cured if the complete remission can be sustained for 2 years or more. Paradoxically, these tumors may have a better prognosis than indolent lymphomas if they are aggressively and appropriately treated.[17,18]

In our series, 37.3% of the large cell lymphomas were the T-cell type. This is considerably higher than the frequencies reported in most of the studies (Table 3). In some geographic locations, notably southwestern Japan, the Caribbean islands, and eastern China, an endemic infection by human T-cell leukemia virus type 1 (HTLV-1) is associated with an increased incidence of a particularly aggressive form of peripheral T-cell lymphoma.[7,19-21] The possibility of a relationship between HTLV-1 infection and increased incidence of T-cell lymphoma in Saudi Arabia is intriguing. Unfortunately, there are no published data available regarding the frequency of HTLV-1 infection in the Saudi population in general, and Saudi patients with malignant lymphoma in particular. In our laboratory, HTLV-1 antibody determinations were performed in 130 consecutive patients with malignant lymphoma. Of these, only seven (5.4%) were positive. These included five T-cell and two B-cell lymphomas. While the numbers of patients studied for HTLV-1 infection in our series are small, the data seem to indicate that HTLV-1 infection may be responsible for at least some of the T-cell lymphomas in this country. Further studies are currently under way at our institution to assess the role of HTLV-1 infection in the pathogenesis of malignant lymphoma in Saudi Arabia.

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References

1. Mahboubi E. Epidemiology of cancer in Saudi Arabia 1975-1985. Ann Saudi Med 1987;7(4):265-76.
2. Gelpi AP. Malignant lymphoma in the Saudi Arab. Cancer 1970;25:892-5.
3. Bin Ahmed OS, Sabbah RS. Childhood non-Hodgkin's lymphoma in Saudi Arabia: clinical features of 100 cases. King Faisal Spec Hosp Med J 1982;2(4):217-23.
4. Sabbah RS, Ali MA, Lewall DB, Aur RJA. Burkitt's lymphoma in Saudi Arabia: clinical, pathological, and epidemiological analyses of 16 cases. King Faisal Spec Hosp Med J 1982;2(2):77-83.
5. The non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. Cancer 1982;49:2112-35.
6. Mann RB, Berard CW. Criteria for cytologic subclassification of follicular lymphomas: a proposed alternative method. Hematol Oncol 1983;1(2):187-92.
7. Harrington DS, Ye YL, Weisenburger DD, et al. Malignant lymphoma in Nebraska and Guangzhou, China: a comparative study. Human Pathol 1987;18(9):924-8.
8. Newell GR, Cabanillas FG, Hagemeister FJ, Butler JJ. Incidence of lymphomas in the US classified by the working formulation. Cancer 1987;59(4):857-61.
9. Pallesen G, Madsen M, Schifter S. Immune marker expression in 53 lymphomas of high-grade malignancy. Histopathology 1983;7(6):841-57.
10. Doggett RS, Wood GS, Horning S, et al. The immunologic characterization of 95 nodal and extranodal diffuse large cell lymphomas in 89 patients. Am J Pathol 1984;115(2):245-52.
11. Aisenberg AC, Wilkes BM, Long JC, Harris NL. Cell surface phenotype in lymphoproliferative disease. Am J Med 1980;68(2):206-13.
12. Rudders RA, Ahl ET, DeLellis RA. Surface marker and histopathologic correlation with long-term survival in advanced large-cell non-Hodgkin's lymphoma. Cancer 1981;47(6):1329-35.
13. Cossman J, Jaffe ES, Fisher RI. Immunologic phenotypes of diffuse, aggressive, non-Hodgkin's lymphomas: correlations with clinical features. Cancer 1984;54(7):1310-7.
14. Hoppe RT. Histologic variation in non-Hodgkin's lymphomas: commentary. Cancer Treat Rep 1981;65(11-12):935-9.
15. Oviatt DL, Cousar JB, Collins RO, et al. Malignant lymphomas of follicular center cell origin in humans: V. Incidence, clinical features, and prognostic implications of transformation of small cleaved cell nodular lymphoma. Cancer 1984;53(5):1109-14.
16. Miller RW. Recent advances in the epidemiology of leukemia and lymphoma in malignant lymphoma. In: Berard CW, Dorfman RF, Kaufman N, eds. International Academy of Pathology Monograph. Baltimore: Williams and Wilkins, 1987:81.
17. Jaffe ES. Relationship of classification to biologic behaviour of non-Hodgkin's lymphomas. Semin Oncol 1986;13(4, suppl 5):3-9.
18. Skarin A. Diffuse aggressive lymphomas: a curable subset of non-Hodgkin's lymphomas. Semin Oncol 1986;13(4, suppl 5):10-25.
19. Uchiyama T, Yodoi J, Sagawa K, et al. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 1977;50(3):481-92.
20. Jaffe ES, Blattner WA, Blayney DW, et al. The pathologic spectrum of adult T-cell leukemia/lymphoma in the United States: human T-cell leukemia/lymphoma virus-associated lymphoid malignancies. Am J Surg Pathol 1984;8(4):263-75.
21. Catovsky D, Greaves MF, Rose M, et al. Adult T-cell lymphoma/leukemias in blacks from West Indies. Lancet 1982;1(8273):839-43.

TINEA VERSICOLOR IN THE EASTERN PROVINCE OF SAUDI ARABIA

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تم فحص مامجموعه ١١٥٠ حالة من حالات اشتبه فيها بالنخالية المبرقشة سريريًا في مستشفى الدمام المركزي من منطقة جغرافية تتوافر فيها عدة عوامل مؤهبة. شكل المرضى السعوديون ٦٦ر٨٪ من الحالات المفحوصة. وكان الجنسان ممثلين بالتساوي وتراوحت أعمار المصابين من شهر واحد إلى ٦٥ سنة كما تراوحت مدة المرض من أسبوع واحد إلى ٢٠ سنة، وتأكد التشخيص السريري لدى ١١٠٢ مريض (٩٥ر٨٪) بالفحص تحت ضوء «وود» وفحص حتاتات الجلد تحت المجهر. وعولج المرضى بمضادات الفطور الموضعية من صنف الأيميدازول (مشتقات الميكونازول أو الكلوتريمازول) أو مستعلق كبريتيد السلينيوم أو الكيتوكانازول بطريق الفم وذلك تبعا للنتائج المجهرية وأعطى العلاج نتائج متفاوتة.

A total of 1150 clinically suspected cases of tinea versicolor were examined in Dammam Central Hospital in a geographic region where many predisposing factors exist. Saudi patients comprised 66.8% of the examined cases. Both sexes were equally represented, and their ages ranged from 1 month to 65 years. The duration of the disease ranged from 1 week to 20 years. Clinical diagnosis was confirmed by examination of the patients under Wood's light and by direct microscopy of skin scrapings in 1102 cases (95.8%). Treatment by topical antifungal imidazole agents (clotrimazole or miconazole derivatives), selenium sulfide suspension, or oral ketoconazole was applied, depending on microscopic findings, and yielded varying results.

The Eastern Province of Saudi Arabia comprises many nationalities and socioeconomic standards. The year-round humidity and temperature of the region are favorable conditions for the formation of tinea versicolor infections. Yet, only two studies have been done (both by us) about tinea versicolor infections in the area, one in children[1] and one in adults.[2] This article describes a series of 1150 patients attending the dermatology outpatient clinic of Dammam Central Hospital from April 1984 to January 1988.

Patients and Methods

Patients clinically suspected of having tinea versicolor were examined. For microscopic examination, skin scrapings from the affected site were examined in potassium hydroxide-dimethyl sulfoxide mount.

For treatment of proved cases, several regimens were used. Acute cases and patients with single areas of infection were treated by topical application of an antifungal imidazole agent (clotrimazole or miconazole derivatives) twice daily for 6 to 8 weeks. For chronic cases with widespread infection, selenium sulfide suspension in 2.5% concentration was used in addition to the imidazole agent. The suspension was applied either daily for 5 to 10 minutes on 21 consecutive days or for 12 hours and then washed off and repeated twice weekly for 6 to 8 weeks.[3]

Sixty patients with extensive and/or frequently

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recurring lesions of tinea versicolor were treated with oral ketoconazole, 200 mg once a day, before breakfast for 10 days. Liver function studies before and at the end of treatment included aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase. Diagnostic procedures were repeated at 10 days, 20 days, and 30 days after starting treatment.

Results

A total of 1150 patients were examined. Both sexes were about equally represented (48.2% males and 51.8% females). Saudis comprised 66.8% of the patients, Yemenis, 9.9%, and Egyptians, 9.5%; the balance of patients were from 20 other African, Asian, and Middle Eastern countries. One hundred eleven patients (9.6%) were children under 12 years old, and 1039 patients (90.4%) were adults, mostly between 20 and 45 years old. The duration of disease ranged from 1 week to 20 years.

Of the 1150 patients clinically suspected of having tinea versicolor, 1102 patients (95.8%) were positive by Wood's light examination and by direct microscopy for *Malassezia furfur* (short hyphal elements and large spores) from either depigmented scaly lesions (Figure 1) or hyperpigmented skin lesions (Figures 2 and 3). Many of the 1102 proved cases were recurrent with widespread infection.

For acute and single areas of infection, treatment with topical application of an imidazole agent showed satisfactory results without recurrence. However, recurrence was observed in many of the patients with widespread infection who were treated with selenium sulfide suspension in addition to the imidazole agent.

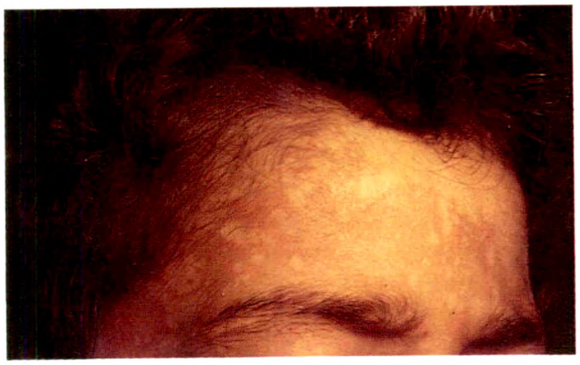

FIGURE 1. Tinea versicolor (hypopigmented form) on the face of a 12-year-old male.

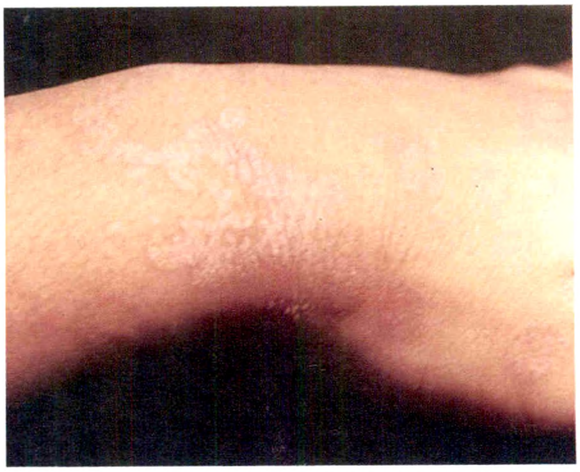

FIGURE 2. Limited form of tinea versicolor (hyperpigmented) in left hand of an 18-year-old female.

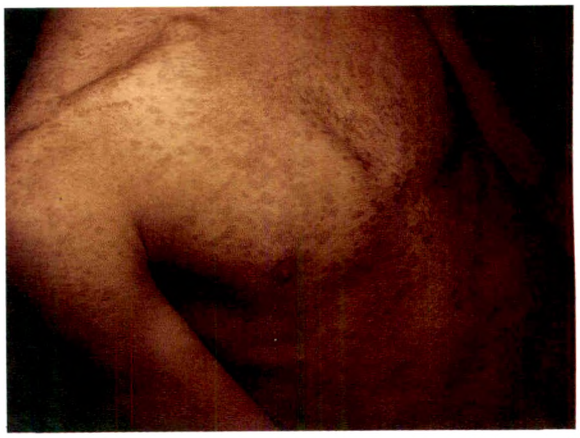

FIGURE 3. Extensive tinea versicolor lesions (hyperpigmented form) in 17-year-old male.

Of the 60 patients treated with ketoconazole, 45 patients provided mycological, clinical, and liver function evaluation data both before and after treatment. Clearance of infection 20 days after completion of therapy was observed in all of them (Figures 4 and 5). No patient complained of adverse effects of the treatment, and results of liver function evaluations were also within normal limits before and after treatment. In patients with hypopigmented lesions and in some with hyperpigmented lesions, discoloration usually persisted, but no fluorescence or fungi were present in the lesions. Of the 45 patients who completed the study, five (11%) returned to the clinic 6 to 9 months later complaining of relapse.

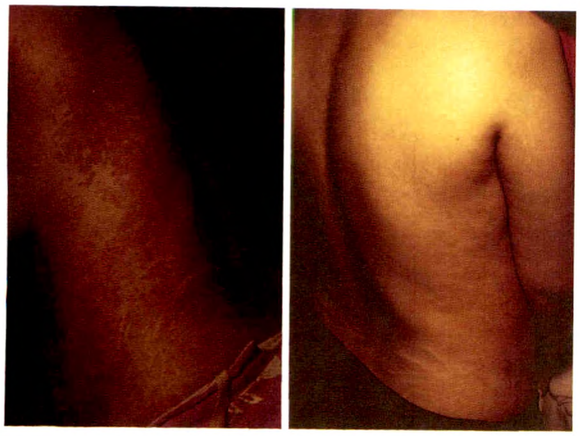

FIGURE 4. Tinea versicolor (hyperpigmented form) in a 25-year-old woman before (left) and after (right) treatment with ketoconazole. Only postinflammatory hyperpigmentations remain.

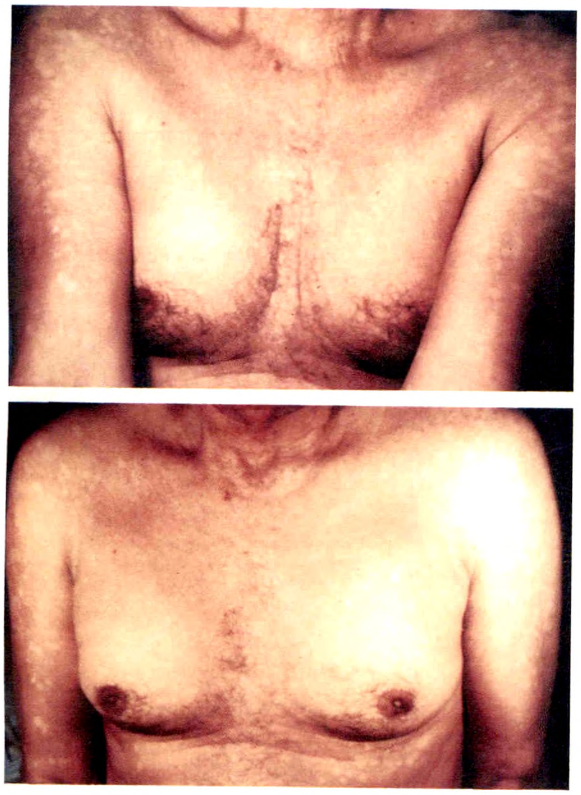

FIGURE 5. Tinea versicolor (hypopigmented form) in a 60-year-old before (above) and after (below) treatment with ketoconazole. Only depigmentations remain.

Discussion

Malassezia furfur is believed to be the mycelial form of *Pityrosporon orbiculare* (*P. ovale*).[4] In the past, all were thought to be distinct fungi, but recent evidence suggests the three are variants of each other.[5,6] Tinea versicolor has a higher incidence in tropical climates and during warmer months in temperate climates than is seen in cooler environments.[7] An increased incidence is also seen in individuals with hyperhidrosis or malnutrition and in those being treated with systemic corticosteroids or other immunosuppressive drugs.[8]

In the Eastern Province of Saudi Arabia exist two of the most influential factors for superficial fungal infections. The mixture of different nationalities with a wide range of socioeconomic standards and high year-round temperature and relative humidity explain the relatively high incidence of tinea versicolor observed in this area. Although these predisposing factors exist, only two studies have been done about these infections in the area. Al-Sogair et al[1] reported that tinea versicolor was seen in 46 (7.1%) of 648 cases of dermatomycosis in children up to the age of 12 years examined in Dammam Central Hospital. The same authors in another study of 1573 clinically suspected cases of superficial mycotic infections and erythrasma in adults reported that tinea versicolor was the predominant fungal infection (32.4% of 1295 cases).[2]

Acute cases and cases with single areas of infection responded successfully to topical antifungal imidazole agents. For chronic cases with widespread infections, selenium sulfide in 2.5% concentration applied topically in addition to the imidazole agent showed unsatisfactory results.

Ketoconazole (an imidazole derivative) is an orally administered antifungal agent[9] reported to be effective against tinea versicolor since 1980.[10-14] In the present study, 60 patients with recurrent and/or extensive lesions were treated with oral ketoconazole, 200 mg once a day for 10 days. Forty-five patients completed the 30-day study period, and all were clear of infection. Mycologically all showed total absence of *M. furfur* elements from the lesions, and clinically skin lesions became completely scaleless with no border elevations. In patients with hypopigmented lesions, discoloration usually persisted but without active disease. No adverse effects were experienced by any patient, and liver function evaluations were also within normal limits before and after treatment for all 45 patients. Lesions recurred in only five patients (11%) 6 to 9 months after the 30-day treatment period.

Faergemann and Djarv[15] stated that the major problem with tinea versicolor is the high rate of recurrence. If the predisposing factors cannot be eliminated, a prophylactic treatment is mandatory. To evaluate the role of ketoconazole as a prophylactic agent, Faergemann and Djarv conducted a double-blind randomized study in which 30 patients were assigned to one of two groups: one group received ketoconazole, 200 mg once a day on 3 consecutive days every month, and the other group received placebo tablets. The patients were followed up for 3 to 11 months. Of the eight patients with recurrences, seven had received placebo and one ketoconazole. According to these investigators, the results suggested that the prophylactic treatment procedure was an effective way to avoid recurrence of tinea versicolor.

At Dammam Central Hospital, for prophylactic treatment, we now give patients with tinea versicolor three 200-mg tablets of ketoconazole a month for at least 6 months. The results will be discussed in a future publication.

References

1. Al-Sogair SM, Al-Humaidan YM, Moawad MK. Superficial mycotic skin infections in children in Eastern Province of Saudi Arabia. Presented at XVII World Congress of Dermatology, Berlin, 24-29 May 1987.
2. Al-Sogair SM, Al-Humaidan YM, Moawad MK. Superficial mycotic skin infections and erythrasma in adults: a regional study of the prevailing species and the patterns of infections in Eastern Province of Saudi Arabia. Presented at XVII World Congress of Dermatology, Berlin, 24-29 May 1987.
3. Rook A, Wilkinson DS, Ebbing FJG, et al. Textbook of dermatology, 4th ed. London: Blackwell Scientific Publications, 1986;2:945.
4. Faergemann J, Fredriksson T. Experimental infections in rabbits and humans with Pityrosporum orbiculare and P. ovale. J Invest Dermatol 1981;77(3):314-8.
5. Faergemann J, Tjernlund U, Scheynius A, Bernander S. Antigenic similarities and differences in genus Pityrosporum. J Invest Dermatol 1982;78(1):28-31.
6. Taplin D. Superficial mycoses. J Invest Dermatol 1976;67(1):177-81.
7. Stein DM. Superficial fungal infections. Pediatr Clin North Am 1983;30(3):545-61.
8. Faergemann J, Fredriksson T. Tinea versicolor: some aspects on etiology, pathogenesis and treatment. Int J Dermatol 1982;21(1):8-11.
9. Thienpont D, Van Cutsem J, Van Gerven F, et al. Ketoconazole—a broad spectrum orally active antimycotic. Experientia 1979;35(5):606-7.
10. Borelli D. Treatment of pityriasis versicolor with ketoconazole. Rev Infect Dis 1980;2:595.
11. Jolliffe DS, Ngai YL. Systemic treatment of tinea versicolor with ketoconazole in forty-four patients. Clin Exp Dermatol 1981;6(6):625-8.
12. Urcuyo FG, Zaias N. The successful treatment of pityriasis versicolor by systemic ketoconazole. J Am Acad Dermatol 1982;6:24-5.
13. Heel RC, Brogden RN, Carmine A, et al. Ketoconazole: a review of its therapeutic efficacy in superficial and systemic fungal infections. Drugs 1982;23:1-36.
14. Hay RJ, Midgeley G. Short course ketoconazole therapy in pityriasis versicolor. Clin Exp Dermatol 1984;9(6):571-3.
15. Faergemann J, Djarv L. Tinea versicolor: treatment and prophylaxis with ketoconazole. Cutis 1982;30(4):542-5.

BEHCET'S DISEASE IN SAUDI ARABIA

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تم فحص ستة وأربعين مريضا يعانون من داء بهجت. بلغ عدد السعوديين منهم سبعة وثلاثين والعرب غير السعوديين تسعة. كانت نسبة الذكور إلى الإناث تعادل ٤ر١ : ١. وبلغت نسبة من يعانون من تقرحات فمية ١٠٠٪، وتقرحات تناسلية ٩١٪، واصابات في العين ٦٥٪، وآفات جلدية ٦١٪، واصابات مفصلية (غير تآكلية) ٥٩٪، وتظاهرات في الجهاز العصبي المركزي ٣٥٪، واصابات معدية معوية ٢٦٪، وآفات وعائية ٢٦٪، ومشكلات نفسية ١١٪، واصابات رئوية ١١٪. أصيب مريض واحد فقط بداء كلوي والذي تم التأكد من صحته عن طريق أخذ خزعة. كان نمط المستضدات السطحية للكريات البيضاء HLA لدى ٧٢٪ من المرضى ايجابيًا بالنسبة للمستضد HLA - B5 (51)

Forty-six patients with Behcet's disease were studied. Of those, 37 were Saudi and 9 were non-Saudi Arabs. Male-to-female ratio was 4.1:1. One hundred percent had mouth ulcers, 91% genital ulcers, 65% ocular involvement, 61% skin lesions, 59% joint involvement (nonerosive), 35% central nervous system manifestations, 26% gastrointestinal involvement, 26% vascular lesions, 11% psychiatric problems, and 11% pulmonary involvement. Only one patient had renal involvement which was documented by biopsy. In 72% of the patients, HLA-B5(51) was positive.

Behcet's disease was first described in 1937 by a Turkish dermatologist, Hulusi Behcet,[1] as a triad of oral and genital ulcers and uveitis. Later the scope of the disease widened to include other manifestations, such as cutaneous vasculitis, meningoencephalitis, synovitis, and alimentary tract involvement. There are various diagnostic criteria for the disease. O'Duffy postulated the major criteria.[2,3] In 1969, Mason and Barnes suggested a series of major and minor criteria.[4] The disease is most common in the Mediterranean Basin, Middle East, and Japan, with incidence varying from 1/10,000 population at Hokkadim in Japan to 2.1/100,000 in Kuwait. The disease is much less common in Europe and the United States with incidence of 1/300,000 in Minnesota.

Not much attention has been paid to Behcet's disease in Saudi Arabia, and we are describing 46 patients who attended various clinics in King Faisal Specialist Hospital and Research Centre (KFSH&RC) and King Khalid University Hospital (KKUH).

Patients and Methods

Forty-six patients with Behcet's disease were seen in KFSH&RC and KKUH in Riyadh during the period from 1979 through 1987. They presented to various clinics depending on the manifestations of the disease.[5] Twenty patients were followed prospectively in the clinics and underwent full clinical examinations by us, as well as by an ophthalmologist, a dermatologist, and other physicians. The data for the rest of the patients were taken from hospital charts.

The following determinations were made in most of the patients: complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive

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protein, immunoglobulin, alpha-naphthoflavone antinuclear factor, rheumatoid factor (RF), serologic test for syphilis, prothrombin time (PT) and partial prothrombin time (PTT), urinalysis, hepatic and renal profiles, complement (C3, C4, CH_{50}), electrocardiogram (ECG), and various radiologic examinations. Thirty patients had HLA typing. Every effort was made to rule out conditions similar to Behcet's disease, especially for those patients who had vascular manifestations of the central nervous system or with gastrointestinal symptoms.

Results

Of the 46 patients, 37 were male and 9 female, giving a male-to-female ratio of 4.1:1. Their ages ranged from 16 to 51 years, with an average age of 31.5. The duration of illness varied from 4 months to 13 years, with a mean of 6.4 years. All the patients in our study fulfilled the Mason and Barnes criteria,[4] and patients with "incomplete" disease were excluded. Table 1 summarizes details of the patients.

Mouth Ulcers

Mouth ulcers were present in all of our patients (Figure 1). The ulcers varied in size and shape from small ulcers in the buccal mucosa to extensive ulcers from the lips down to the fauces. The lesions were quite painful. No esophageal ulcers were seen. These ulcers were indistinguishable from common recurrent aphthous ulcers that occurred in 20% of the population.[6,7] The duration of these lesions varied between 10 and 20 days, and the frequency of attacks varied between three and seven per year. No scarring was seen in our patients following oral ulcers.

Genital Ulcers

Genital ulcers were present in 42 (91%) of our patients. They were multiple and painful, with a recurrence rate of one to three per year. Most ulcers left scars after healing. In most patients the genital ulcer was by history only, and scars were documented in the hospital charts. Constitutional symptoms were not present in most of the patients with active orogenital ulcers. Epididymo-orchitis was not documented in any patient.

Ocular Lesions

Ocular symptoms and signs were present in 30 (65%) of the patients. Symptoms varied from itching and redness to severe pain and blindness. Visual problems caused the patients to seek treatment early. Exacerbation of ocular symptoms was not associated with increased disease activity in other organs, such as oral or genital ulceration. Table 2 summarizes the types of ocular involvement.

Skin Manifestations

Skin lesions were present in 28 (61%) of our patients. A skin lesion was not the presenting feature in any patient and was always preceded by orogenital ulcer or other manifestations. Unfortunately, a pathergy test was done in only a few patients who returned for follow-up, and it would be difficult to assess its significance as a diagnostic parameter. Some of the patients had more than one lesion.[8] Table 3 reflects the scope of skin lesions.

Joint Involvement

Twenty-seven patients (59%) had joint involvement varying from single arthralgia to florid arthritis resembling rheumatoid arthritis.[4,9] Arthralgia without arthritis was present in 16 patients and was generalized in only four patients. Joint involvement was associated with other manifestations of the disease, especially orogenital ulcers, skin lesions, and systemic symptoms. Arthritis was present in 12 patients, and the most commonly involved joints were knees, ankles, and metacarpophalangeal joints. There was knee joint effusion in five patients, with exudate aspirated. Morning stiffness was present, but unlike rheumatoid arthritis, the symptom did not improve as the day progressed. The ESR was elevated in all patients with active disease, and RF was negative in all the patients. The temporomandibular joint was involved in one patient (no. 19, Table 1). Many patients had multiple joint involvement; however, the sacroiliac joint was not affected in any patient. Table 4 summarizes joint involvement.

TABLE 1. *Clinical data on patients in Saudi Arabia with Behcet's disease.*

Patient no.	Age (y)	Sex	Duration of illness (y)	Manifestation										
				Oral	Genital	Ocular	Skin	Vascular	Joints	Psychiatric	CNS	GI	Pulmonary	Renal
1	32	M	13	+	+	+	+	−	+	−	−	−	−	−
2	44	M	6	+	+	−	+	+	+	−	−	−	+	−
3	32	M	4	+	+	+	−	−	−	−	+	−	−	−
4	46	M	12	+	+	−	−	−	−	−	+	−	−	−
5	32	M	10	+	+	+	−	−	−	−	+	−	−	−
6	37	M	5	+	+	+	+	−	−	−	+	−	−	−
7	38	M	7	+	+	+	+	+	−	−	−	−	−	−
8	23	M	4	+	+	−	+	−	+	−	−	−	−	−
9	50	M	13	+	−	+	−	−	+	−	−	−	−	−
10	22	F	8	+	+	+	+	−	−	−	+	−	−	−
11	35	M	10	+	+	−	+	+	+	−	−	+	−	−
12	19	F	2	+	+	+	+	+	+	−	+	+	−	−
13	29	M	11	+	+	+	+	−	+	−	+	−	−	−
14	21	M	6	+	−	+	−	−	−	−	+	−	−	−
15	30	F	2	+	+	−	−	+	+	−	−	−	+	−
16	40	M	8	+	+	+	+	−	−	−	+	+	+	−
17	37	M	6	+	+	+	+	−	+	−	−	−	−	−
18	38	M	5	+	+	−	+	−	+	−	−	−	−	−
19	28	M	8	+	+	+	+	−	+	−	−	−	−	−
20	51	M	3	+	+	+	+	−	+	−	−	−	−	−
21	28	F	6	+	+	+	+	−	+	+	−	+	−	−
22	34	M	8	+	+	−	−	+	−	+	+	+	−	−
23	27	M	7	+	−	+	−	−	−	−	+	+	−	−
24	39	M	9	+	+	+	+	−	+	−	+	+	+	−
25	49	F	13	+	+	−	+	−	+	−	−	−	−	−
26	26	M	4	+	+	+	−	−	+	−	−	−	−	−
27	33	F	6	+	+	+	+	−	+	+	−	−	−	−
28	23	M	5	+	+	+	+	−	+	−	−	−	−	−
29	39	M	16	+	+	−	+	+	+	−	−	−	+	−
30	47	F	10	+	+	−	+	+	+	−	−	+	−	−
31	25	M	5	+	+	+	−	−	−	−	−	+	−	+
32	26	M	4	+	+	−	+	−	−	−	+	+	−	−
33	21	M	2	+	+	−	+	−	+	−	−	−	−	−
34	24	M	3	+	+	+	−	−	−	−	−	−	−	−
35	29	M	3	+	+	−	+	+	+	−	−	−	−	−
36	16	M	3	+	+	+	−	−	+	−	−	−	−	−
37	30	M	10	+	+	−	−	−	−	+	+	−	−	−
38	24	M	4	+	+	+	+	−	−	+	−	+	−	−
39	26	M	1	+	−	+	−	−	−	−	+	+	−	−
40	28	M	0.4	+	+	+	+	−	+	−	−	+	−	−
41	16	F	4	+	+	−	+	−	+	−	−	−	−	−
42	37	M	5	+	+	+	+	+	−	−	−	−	−	−
43	24	M	3	+	+	+	−	−	+	−	−	−	−	−
44	30	M	3	+	+	+	−	−	−	−	−	−	−	−
45	32	M	7	+	+	−	−	−	+	−	+	−	−	−
46	31	F	4	+	+	+	−	−	−	−	−	−	−	−
			Total %	46 (100)	42 (91)	30 (65)	28 (61)	12 (26)	27 (59)	5 (11)	16 (35)	12 (26)	5 (11)	1 (2)

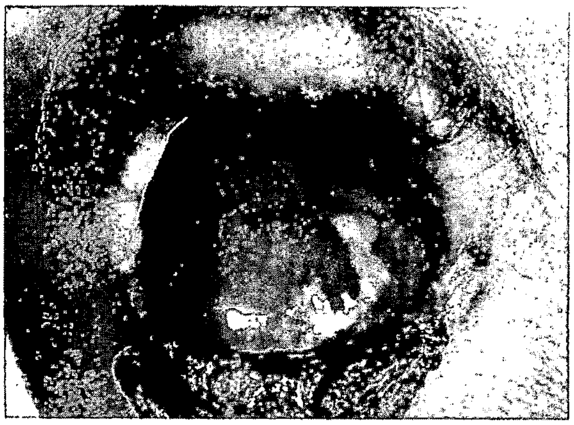

FIGURE 1. Patient 29, showing extensive oral ulceration.

TABLE 2. *Ocular lesions in 30 patients with Behcet's disease.*

Type of ocular lesion*	No. of patients
Anterior segment (26 patients)	
Iridocyclitis	23
Conjunctivitis	3
Posterior segment (15 patients)	
Retinal vasculitis	6
Macular edema	1
Papillitis	4
Choroiditis	6
Detachment	5
Complications (6 patients)	
Cataract	2
Glaucoma	1
Unilateral blindness	2
Bilateral blindness	1

*Some patients had more than one type of ocular involvement.

TABLE 3. *Skin manifestations in 28 patients with Behcet's disease.*

Type of skin lesion	No. of patients
Pustular lesion	14
Erythema nodosum	8
Superficial thrombophlebitis	4
Acneiform lesion	4
Folliculitis	2
Bullous lesion	1
Nonspecific lesion	1

*Some patients had more than one type of lesion.

TABLE 4. *Joint involvement in 27 patients with Behcet's disease.**

Arthropathy	No. of patients
Arthralgia (16 patients)	
Generalized	4
Knees	11
Ankles	2
Elbows	2
Arthritis (12 patients)	
Knees	10
Metacarpophalangeal joint	5
Proximal interphalangeal joint	3
Ankles	5
Wrists	3
Shoulders	2
Elbows	3
Temporomandibular joint dysfunction	1

*Some patients had multiple joint involvement.

Neurologic Manifestations

Neurologic symptoms were present in 16 patients (35%) and varied from simple headache to quadriparesis. Two patients presented with headache, blurred vision, nausea and vomiting, as well as papilledema. Both were diagnosed as having intracranial hypertension based on evidence obtained by computed tomographic (CT) scan and cerebrospinal fluid (CSF) opening pressures of 320 mm Hg in patient 12 and 345 mm Hg in patient 22. Neither had factors predisposing to benign intracranial hypertension, and both responded well to dexamethasone treatment.

Patient 23 presented with acute ascending paralysis with intercostal involvement and required assisted ventilation. The CSF showed increase in protein. Lymphocytosis responded well to management and was diagnosed as Guillain-Barre syndrome. Patients 5 and 13 had paraplegia with sensory level at T-10 and T-2, respectively. In patient 5, the CT myelogram showed a syringomyelia-like cavity at T5-6, compatible with infarction. However, in patient 13 results of all investigations were normal. Three patients had paraplegia, and one had quadriplegia without a sensory level. The CT myelogram, CSF examination, evoked responses, and electroencephalogram were normal. Thus, these manifestations were attributed to brain stem involvement by Behcet's disease.

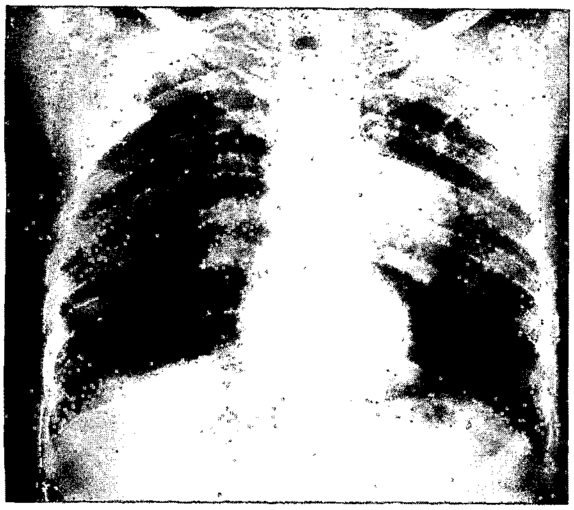

FIGURE 2. Chest x-ray film for patient 2 demonstrating right hilar mass, proved later to be pulmonary artery aneurysm.

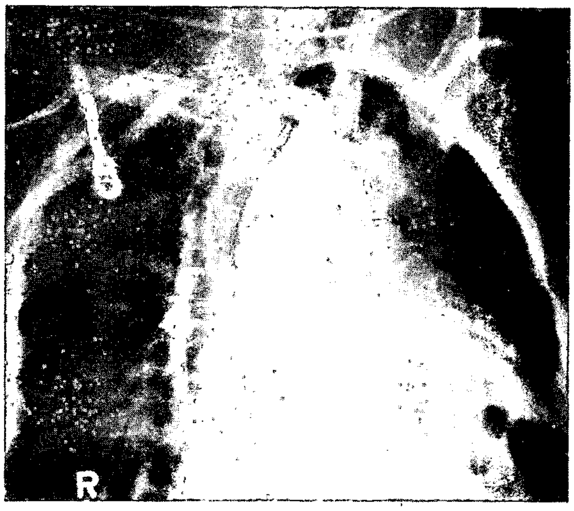

FIGURE 3. Aortogram for patient 24 showing aortic aneurysm.

Vascular Involvement

Vascular symptoms occurred in 12 patients (26%). Migratory thrombophlebitis was seen in four patients. These patients presented with painful erythematous cordlike lesions which lasted for a few days, leaving behind skin discoloration which later faded. During follow-up, these patients developed deep vein thrombosis and inferior vena caval obstruction. Three patients had inferior vena caval obstruction with prominent collateral vein over the abdomen with the other collaterals patent on venogram. One patient had hepatic vein thrombosis and presented a picture compatible with Budd-Chiari syndrome. Four patients had thrombosis limited to the leg veins.

Patient 2 had a mass on chest x-ray film, hemoptysis, cough, and pleuritic chest pain, and was later diagnosed as having pulmonary artery aneurysm (Figure 2).

Patient 24 had acute chest pain of a pleuritic nature and a shadow on chest x-ray film. An aneurysm was suspected, and aortogram showed aneurysm of descending thoracic artery with clot filling (Figure 3). The descending thoracic artery was resected, but 3 years later the aneurysm recurred.

Patient 38, who was only 24 years old, presented with acute central chest pain radiating to his left arm and associated with sweating, nausea, and vomiting. Acute myocardial infarction was proved by ECG and cardiac enzyme levels. No underlying predisposing factor was present, and this was attributed to vasculitis of Behcet's disease.

Laboratory Investigations

Five patients (two male and three female) had anemia. One female had iron-deficiency anemia, and the others had anemia of chronic illness. The ESR was elevated during exacerbation of the disease, and the highest value was 130 mm/h. Levels of platelets and white blood cells were normal in all patients. The antinuclear antibodies, rapid plasma reagin, and RF were always negative.

Urinalysis was abnormal in only one patient (no. 31) who showed proteinuria and hematuria. Renal biopsy revealed mesangial proliferative glomerulonephritis.

The PT and PTT were prolonged in three patients who were on anticoagulant therapy at the time they presented to us. Complement level C3, C4, and CH_{50} were normal in all 46 patients. Immunoglobulins IgG6, IgM1, and IgM5 were elevated in 12 patients.

Thirty-two patients had HLA typing (Table 5). Twenty-three patients (72%) had HLA-B5(51), and out of these 15 (66%) had uveitis and 13 (60%) had arthritis. There is, therefore, a strong correlation between uveitis, arthritis, and HLA-B5(51).

TABLE 5. *HLA typing of 32 patients with Behcet's disease.*

Patient no.	HLA typing									
3	A2		B5(51)X	B35						
4	A28		B5(51)'							
5	A10(26)	A19(31)	B5(51)X	B35						
7	A10	A28		B35		C4				
8	A2	A28	B5(51)	B17						
9	A2	A3	B5(51)	B17		C3				
10	A19		B5(51)							
11	A2	A10(26)	B8	B17		C7				
12	A30	A31	B18	B37		C3	C7			
13	A2	A9(23)	B5(51)			C3				
14	A1	A10(19)	B5	B17						
15	A2		B35			C2	C4	D4	DW6	
16	A11	A28	B21							
17	A3	A10(19)	B5							
18	A1	A28	B5(51)	B219						
19	A2		B5(51)							
20	A2	A19	B5(51)							
21	A10		B5(51)			CW2				
25	A1	A2	B5(51)			C4				
27	A11	A39	B5(51)							
28	A10	A28	B5(51)					D5		
31	A1	A2	B41			CW7	D3W6	DQW1,2	DRW52	
32	A3	A19(31)	B5(51)			C3		D1.4	DQW1.3	HRW52,53
34	A10(26)	A28	B15(63)	B8BW46		CW7		DR2	DR3	
35	A2	A3	B5(51)	B15						
36	A11	AW31	B13	B15(63)	BW6	CW1		DR3	DR7	
39	A3	A9(24)	B15(62)	B22(55)		CW1	CW7	DR2	DQW1	
40	A2	A3	B5(51)	B35BW4		CW5		DR2	DR4	
41	A1	A2	B5(51)	B18BW4.7		CW7		DR1	DR2	
42	A2	A19(32)	B5(51)			CWX				
44	A19		B5(51)					DRQ52		
46	A10		B5(51)					DR2		

Discussion

Our study bears an interesting similarity to two other studies from the region.[7,10] Like the others, our study confirms that Behcet's disease is not an uncommon disease in this region,[9] and the clinical manifestations also appear to be similar.[7,9-12]

However, interesting differences are also present. Neurologic manifestations were greater in severity and frequency in our study than in the others.[3,11,13-15] On the other hand, there appear to have been more psychiatric manifestations in Kuwait[14] than either Riyadh or Iraq.[15] These differences may reflect an interest in the respective specialties in the different institutions. However, since all three studies have come from referral hospitals,[13-15] the differences could to some extent be real.

Many of the neurologic manifestations in our study, as well as in the other studies, were attributable to pyramidal tract lesions, possibly caused by impairment of arterial supply.[16] The two patients (nos. 12 and 22) with raised intracranial pressure and no focal lesions probably had intracranial venous sinus thrombophlebitis. To our knowledge, the syringomyelia-like lesion seen in patient 5 has not been documented before and could also have followed chronic ischemia. The ascending paralysis similar to Guillain-Barre syndrome seen in patient 23 also has not been reported previously with Behcet's disease. The nature of its pathogenesis is not easily determined.

Though no patients with inferior vena caval thrombosis were observed in the Kuwait study,[14] we encountered four such patients, including three who presented with it and one who developed it subsequently. Arterial involvement was seen in three of our patients in contrast to two from Kuwait[14] and none from Iraq.[15] The arterial aneurysm seen in two of these, though rare, is well documented.[12,17]

The acute myocardial infarction seen in patient 38, however, does not appear to have been documented before. The etiology of vascular occlusions in Behcet's disease is probably multifactorial.[16,18,19] Inflammation of the vessel wall is a major contributor. A hypercoagulable state and decreased fibrinolysis are other possible factors promoting occlusive vascular events in Behcet's disease.

We recorded a 70% incidence of HLA-B5(51), which was very similar to that in Iraq,[15] Turkey,[20] and Japan,[21] though it was not found in Britain.[11] This figure contrasts with the 26% seen in normal persons in this population. However, information on the pathergy test in this study was too inadequate to look for a correlation between it and the presence of HLA-B5(51) as others have done.

In contrast to the study by Rosenthal et al,[10] this study showed that microscopic hematuria and/or proteinuria are rare in patients with Behcet's disease. Only one patient had proteinuria and hematuria, and renal biopsy showed moderate mesangial proliferative glomerulonephritis. Both Hamza et al[22] and Oshima and Shimuzi[12] reported renal biopsies with normal appearance or only minor pathologic changes, fibrosis around arterioles, and glomerular hypercellularity.

References

1. Behcet H: Geschwure am Mund. Dermatol Wochenschr 1937;105:1152-7.
2. Jorizzo JL, Hudson RD, Schmalstieg FC, et al. Behcet's syndrome: immune regulation, circulating immune complexes, neutrophil migration, and colchicine therapy. J Am Acad Dermatol 1984;10:205-14.
3. O'Duffy JD, Goldstein NP. Neurologic involvement in seven patients with Behcet's disease. Am J Med 1976;61:170-8.
4. Mason RM, Barnes CG. Behcet's syndrome with arthritis. Ann Rheum Dis 1969;25:95-103.
5. Berlin C. Behcet's disease as a multiple symptom complex: report of ten cases. Arch Rheumatol 1960;82:127-73-9.
6. Lehner T. Oral ulceration and Behcet's syndrome: progress report. Gut 1977;18:491-511.
7. Rogers RS. Recurrent aphthous stomatitis: clinical characteristics and evidence for an immunopathogenesis. J Invest Dermatol 1977;69:499-509.
8. Nazzaro PO. Cutaneous manifestation of Behcet's disease: clinical and histological findings. Proceedings of 15th International Symposium on Behcet's Disease, Rome, 1965. New York: Karger, 1966:15-41.
9. Madkour M, Kudwah F. Behcet's disease (letter). Br Med J 1978;2:1786.
10. Rosenthal T, Weiss D, Gafni J. Renal involvement in Behcet's syndrome. Arch Intern Med 1978;138:1122-4.
11. Chamberlain MA. Behcet's syndrome in 32 patients in Yorkshire. Ann Rheum Dis 1977;36:491-9.
12. Oshima Y, Shimizu T. Clinical studies on Behcet's syndrome. Ann Rheum Dis 1963;22:36-45.
13. Wolf S, Schotland DL, Philip LL. Involvement of the nervous system in Behcet's disease. Arch Neurol 1965;12:315-25.
14. Mousa AM, Marafie AA, Rifai KM, et al. Behcet disease in Kuwait and Saudi Arabia. Scand J Rheumatol 1986;15:310-32.
15. Al-Rawi ZS, Sharquie KE, Khalifa SJ, Al-Hadithi FM. Behcet disease in Iraqi patients. Ann Rheum Dis 1986;45:987-90.
16. Schotland DL, Wolf SM, White HH, Dubin HV. Neurological aspects of Behcet disease. Am J Med 1963;34:544.
17. Mowat AG, Hothersall TE. Gangrene in Behcet's syndrome. Br Med J 1969;2:636.
18. Davies JD. Behcet's syndrome with haemoptysis and pulmonary lesions. J Pathol 1973;109:351-6.
19. Slavin RE, de Groot WJ. Pathology of the lung in Behcet's disease. Am J Surg Pathol 1981;5:779-84.
20. Takano M, Miyajima T, Kiuchi M, et al. Behcet's disease and the HLA system. Tissue Antigen 1976;8:95-9.
21. O'Duffy JD, Lehner T, Barnes CG. Close association HLABW51, Mt2 and Behcet's disease: summary of the international conference on Behcet's disease, Tokyo, Japan, 1981. J Rheumatol 1983:154-8.
22. Hamza M, Zribi A, Chadli A, Benayed H. La maladie de Behcet: etude de 22 cas. Nouv Presse Med 1975;4:563-6.

PERIVENTRICULAR/INTRAVENTRICULAR HEMORRHAGE IN THE NEWBORN

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أجريت دراسة استعادية على مدى ٤ سنوات (١٤٠٤ ـ ١٤٠٧هـ) شملت ما مجموعه ١١٠٥٠ ولادة وأظهرت أن وقوع النزف حول البطينات الدماغية أو داخلها لدى الخدج المولودين في مستشفى الملك خالد التعليمي كان بنسبة ٢٠ر٩٪ لمن ولدوا بعد حمل دام خمسة وثلاثين أسبوعا أو أقل و٤٠ر٨٪ لمن كان وزنهم ١٥٠٠غم فما دون حين الولادة. ولدى ترتيب جداول الوقوع والدرجة والمرافقات والنتيجة لدى الخدج الذين عانوا من هذا النزف، وجد أن الدرجة الأولى هي الغالبة وأن النزف أكثر تواترا لدى الخدج الذين ولدوا بين الأسبوعين السادس والعشرين والثلاثين من الحمل (٤٢ر٥٪) ولدى من تراوح وزنهم بين ٥٠٠ و ٧٥٠غم حين الولادة (٤٢ر٩٪). وكانت متلازمة ضائقة التنفس ترافق النزف لدى ٨١ر٣٪ من الخدج المصابين بالنزف.

In a retrospective study spanning 4 years (1404-1407H) and including a total of 11,050 births, the incidence of periventricular/intraventricular hemorrhage (PVH/IVH) in infants born at King Khalid University Hospital at or before 35 weeks of gestation was 20.9% and in those weighing 1500 g or less at birth was 40.8%. Incidence, grade, associations, and outcome of infants suffering PVH/IVH were tabulated. Most common was grade 1 hemorrhage; PVH/IVH was most frequently seen in infants born between 26 and 30 weeks' gestation (42.5%) and in those weighing between 500 and 750 g (42.9%) at birth. Respiratory distress syndrome was associated in 81.3% of the infants with PVH/IVH.

Improved neonatal intensive care during the past decade has resulted in the survival of many premature infants who formerly would have died.[1] With enhanced perinatal and neonatal care being offered in the Kingdom, survival of preterm and very low-birth-weight infants has improved considerably,[2] but akin to reports from the developed world, a large number of infants weighing 1500 g or less at birth die, and many more are handicapped due to periventricular/intraventricular (PVH/IVH) hemorrhage.[3-7]

This report summarizes our experience over a 4-year period (1404-1407H) of PVH/IVH at the neonatal service of the King Khalid University Hospital (KKUH), Riyadh.

Patients and Methods

The neonatal intensive care unit (NICU) is a 22-bed tertiary care unit. It serves infants born at KKUH and at King Abdul Aziz University Hospital, Riyadh; however, only infants born at KKUH have been included in this analysis. The annual delivery rate at KKUH increased from 1709 in 1404H to 3732 in 1407H.

All infants born at or before 35 weeks' gestation are admitted to the NICU. Gestation is assessed by maternal dates, antenatal ultrasonographic assessment of fetal biparietal diameter, abdominal circumference, and femur length. Postnatal gestational assessment is performed within the

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first 24 hours of birth using Ballard's scoring system.[8]

A total of 236 infants were born before 35 weeks of gestation out of the total 11,050 births over these 4 years (2.1%). Of the 236 infants, 230 had cranial ultrasonographic examination. These were usually performed at 3 and 7 days of age. All sonograms were performed using Hewlett-Packard real-time sector scanner with a 5-MHz Phasedarry transducer. All examinations were performed in the NICU. No sedation was used. Standard sonographic techniques, including axial and occipital views, were used to obtain sections in coronal and sagittal planes.

Intracranial hemorrhage was classified according to Papile.[9] Patients with PVH/IVH were followed by once-weekly ultrasound scans of the brain until discharge from the NICU or their death. Ventricular dilatation was determined by daily occipitofrontal head circumference measurement and repeat ultrasound examination. Whenever necessary, cranial CT scan was also performed.

Posthemorrhage hydrocephalus was treated by placement of ventriculoperitoneal shunt, which in most cases was carried out after a period of external ventricular drainage. Follow-up after discharge was carried out by us in the high-risk clinic, where gross motor, social, and developmental screening was done. No formal or detailed screening (such as the Griffiths screening) was applied. The follow-up period in this report ranges from 12 months to 4 years.

Results

A total of 236 infants were born at or before 35 weeks of gestation during the study period, giving an incidence of 2.1%. Of these 236 infants, six died prior to any sonographic examination of the brain, so have not been included in the analyses shown in Tables 1 and 2. The overall incidence of PVH/IVH in infants under 35 weeks' gestation was 20.9%, but rose to 40.8% when it was correlated to infants weighing 1500 g or less at birth.

TABLE 1. *Incidence of PVH/IVH in relation to gestational age.*

Gestational age (w)	No.	Grade of PVH/IVH				Total
		I	II	III	IV	
<26	16	0	2 (12.5)	0	3 (18.7)	5 (31.3)
26–30	80	9 (11.3)	3 (3.7)	15 (18.7)	7 (8.7)	34 (42.5)
31–35	134	4 (3.0)	1 (0.7)	2 (1.5)	2 (1.5)	9 (6.7)
Total*	230	13 (5.7)	6 (2.6)	17 (7.4)	12 (5.2)	48 (20.9)

*Total does not include six infants who died prior to any sonographic examination of the brain. Numbers in parentheses are percentages.

TABLE 2. *Incidence of PVH/IVH related to birth weight.*

Birth weight (g)	No.	Grade of PVH/IVH*				Total
		I	II	III	IV	
500–750	14	0	2 (14.2)	1 (7.1)	3 (21.4)	6 (42.9)
751–1000	30	3 (10.0)	2 (6.7)	5 (16.7)	2 (6.7)	12 (40.0)
1001–1500	59	7 (11.9)	2 (3.4)	9 (15.3)	6 (10.2)	24 (40.7)
Total†	103	10 (9.7)	6 (5.8)	15 (14.6)	11 (10.7)	42‡ (40.8)

*Numbers in parentheses are percentages.
†Total does not include six infants who died prior to any sonographic examination of the brain.
‡Six infants born prior to 35 weeks' gestation had birth weight greater than 1500 g, and thus are not included in this table.

Associated diagnoses are shown in Table 3. The most common was respiratory distress syndrome, which was associated with PVH/IVH in 39 of 48 cases (81.3%). Patent ductus arteriosus was associated with PVH/IVH in 21 cases (43.7%). The most frequent presenting feature was pallor (41.7%), followed by seizures (39.6%), but the majority (54.2%) had no clinical signs of cerebral hemorrhage.

Outcome is shown in Figure 1. A total of 16 (33.3%) infants with PVH/IVH died, while 21 (43.7%) survived without any handicap, neurologic or otherwise. The remaining 11 (22.9%) survived with handicap. Fifteen infants (31.3%) required drainage due to posthemorrhage hydrocephalus.

TABLE 3. *Associated diagnoses and most common presenting features (n = 48).*

	No. (%)
Association	
Respiratory distress syndrome	38(81.3)
Need for ventilation	31(64.6)
Patent ductus arteriosus	21(43.7)
Clinical presentation	
Shock	3(6.3)
Pallor	20(41.7)
Apnea	8(16.7)
Hypotension	6(12.5)
Seizures	19(39.6)
Tachycardia	4(8.3)
Bulging fontanelle	10(20.8)
Unexplained acidosis	3(6.3)
None	26(54.2)

*More than one sign or symptoms per infant.

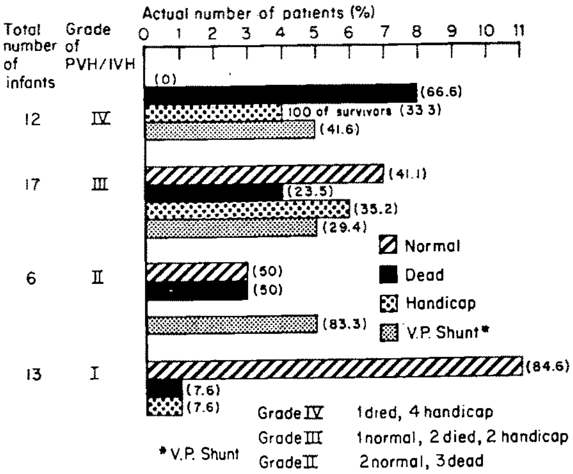

FIGURE 1. Outcome of infants with PVH/IVH.

Discussion

With increasing survival of very low-birth-weight infants, ischemic and hemorrhagic central nervous system lesions have become the major cause of their mortality and morbidity.[3,4,10] PVH/IVH are by far the most important ischemic/hemorrhagic lesions in premature infants. Though incidence of PCH/IVH may be declining,[5,10] prospective studies have consistently reported a 40% to 50% of incidence of IVH in infants weighing 1500 g or less at birth.[3,4,11] At KKUH over a 4-year period, the incidence of PVH/IVH in infants under 35 weeks of gestation at birth was 20.9%, but rose to 40.6% in infants born at or before 30 weeks of gestation. Our incidence of 40.8% of PVH/IVH in infants weighing 1500 g or less is comparable to that reported in the literature.[3,4,10,11]

It is understandable that the incidence of PVH/IVH should be higher in infants under 30 weeks of gestation because of the peculiarity of the blood supply and cerebrovascular physiology at this age.[12,13] Much of the bleeding arises from the germinal matrix. The subependymal germinal matrix is a collection of densely packed glioblastic cells in the ganglia lying over the head and body of the caudate nucleus.[13] The blood supply to the germinal matrix is from the recurrent artery of Heubner, lenticulostriate arteries, and the anterior choroidal artery. In the immature brain (24 to 32 weeks), a substantial proportion of the cerebral blood flow is directed to the germinal matrix until the development of the cerebral cortex assumes prominence (>34 weeks). The vascular endothelial cells of this area are highly dependent on oxidative metabolism, which makes them readily susceptible to hypoxic and/or ischemic insults. Moreover, the high fibrinolytic activity of the germinal matrix tissue allows enlargement of an initially small hemorrhage.[14]

These characteristics explain why hemorrhage arises over the body of the caudate nucleus before 30 weeks' gestation and over the head of the caudate nucleus near the foramen of Monro between 30 to 32 weeks. Since the germinal matrix disappears beyond 32 weeks of gestation, PVH/IVH are rare beyond this gestational age.[13]

There are many other factors such as pressure-passive cerebral blood flow in preterm infants,[13,15] hypoxia and asphyxia,[13] respiratory distress syndrome,[13] positive pressure ventilation,[16] and patent ductus arteriosus.[13] The relative contribution of these factors to the pathogenesis of IVH remains controversial; however, better understanding of these factors and neonatal pathophysiology continues to improve the outlook for these tiny infants.

Most of the therapeutic modalities –phenobarbital,[17,19] ethamsylate,[20] daily lumbar puncture,[11,21] and others[11]–used for the treatment of PVH/IVH and prevention of posthemorrhage hydrocephalus remain inconclusive. The best hope for preventing PVH/IVH lies in reducing the rate of premature deliveries. It is clear from our study that the target should be to reduce the number of infants born weighing 1500 g or less at birth prior to 30 weeks of gestation.

Recent reports[22-24] have shown continued improved outcome of infants even with grade IV PVH/IVH. Unfortunately, we were not very successful with infants who had grade IV PVH/IVH; 66.6% of these infants died and none of those who survived were normal on follow-up. Posthemorrhagic hydrocephalus developed in 41.6%, requiring ventriculoperitoneal shunt operation. However, for other grades of hemorrhage (I-III), the majority of infants (58.3%) were completely normal at follow-up. (One infant died from necrotizing enterocolitis.) The prognosis of PVH/IVH is not uniformly poor, and every effort should be made to provide these infants with optimum care so that they survive with the best possible chance of being normal. The overall handicap rate of 22.9% for all grades of hemorrhage in our group is comparable to other reports,[22-24] though it must be taken with caution as we did not do any formal assessment scoring.

We conclude that PVH/IVH is a major cause of mortality and morbidity of infants born weighing 1500 g or less. The main hope of reducing this human wastage and suffering lies in reducing the incidence of prematurity with better antenatal and perinatal care after delivery by preventing hypoxia, fluctuations in cerebrovascular blood flow, and the injudicious use of hyperosmolar solutions.

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References

1. Haque KN. Outcome of low and very low birth weight infants: a case for regionalization of perinatal care in Saudi Arabia. Ann Saudi Med 1986;6(4):247-51.
2. Haque KN, Bashir O. Perinatal mortality at King Khalid University Hospital, Riyadh. Ann Saudi Med 1988;8(3):190-3.
3. Haque KN. A scheme for better perinatal care in the Kingdom of Saudi Arabia. Saudi Med J 1988;9(3):239-46.
4. Ahmann PA, Lazzara A, Dykes FD, et al. Intraventricular hemorrhage in the high-risk preterm infant: incidence and outcome. Ann Neurol 1980;7(2):118-24.
5. Shinnar S, Molteni RA, Gammon K, et al. Intraventricular hemorrhage in the premature infant. N Engl J Med 1982;306(24):1464-8.
6. Haque KN. Patterns of cerebral palsy in Riyadh, Saudi Arabia. Pak Pediatr J 1986;10(1):1-12.
7. Taha SA, Mahdi AH. Cerebral palsy in Saudi Arabia: a clinical study of 102 cases. Ann Trop Paediatr 1984;4(3):155-8.
8. Ballard JL, Kazmaierk K, Driver MA. A simplified assessment of gestational age (abstract). Paediatr Res 1977;11(4):374.
9. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 g. J Paediatr 1978;92(4):529-34.
10. Harbaugh RE, Saunders RL. Intraventricular hemorrhage in premature infants. In: Contemporary neurosurgery: a biweekly review of clinical neurosurgical practice. 1986;6(3):1-6.
11. Allan WC, Volpe JJ. Periventricular-intraventricular hemorrhage. Pediatr Clin North Am 1986;33(1):47-63.
12. Hambleton G, Wigglesworth JS. Origin of intraventricular haemorrhage in the preterm infant. Arch Dis Child 1976;51(9):651-9.
13. Pape KE, Wigglesworth JS. In: Haemorrhage, ischaemia and the perinatal brain. Philadelphia: JB Lippincott Co, 1979:1-58.
14. Gilles FH, Price RA, Kevy SV, Berenberg W. Fibrinolytic activity in the ganglionic eminence of the premature human brain. Biol Neonate 1971;18:426-32.
15. Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome: relation to the development of intraventricular hemorrhage. N Engl J Med 1983;309(4):204-9.
16. Fitzhardinge PM, Papa P, Arstikaitis M, et al. Mechanical ventilation of infants of less than 1,501 gm birth weight: health, growth and neurologic sequelae. J Pediatr 1976;88(4):531-41.
17. Donn SM, Roloff DW, Goldstein GW. Prevention of intraventricular haemorrhage in preterm infants by phenobarbitone: a controlled trial. Lancet 1981;2(8240):215-7.
18. Morgan ME, Massey RF, Cooke RW. Does phenobarbitone prevent periventricular hemorrhage in very low-birth-weight babies?: a controlled trial. Pediatrics 1982;70(2):186-9.
19. Kuban KC, Leviton A, Krishnamoorthy KS, et al. Neonatal intracranial hemorrhage and phenobarbital. Pediatrics 1986;77(4):443-50.

20. Morgan ME, Benson JW, Cooke RW. Ethamsylate reduces the incidence of periventricular haemorrhage in very low birth-weight babies. Lancet 1981;2(8251):830-1.
21. Mantovani JF, Pasternak JF, Mathew OP, et al. Failure of daily lumbar punctures to prevent the development of hydrocephalus following intraventricular haemorrhage. J Pediatr 1980;97(2):278-81.
22. Pasternak JF, Volpe JJ. Full recovery from prolonged brainstem failure following intraventricular hemorrhage. J Pediatr 1979;95(6):1046-9.
23. Papile LA, Munsick-Bruno G, Schaefer A. Relationship of cerebral intraventricular hemorrhage and early childhood neurologic handicaps. J Pediatr 1983;103(2):273-7.
24. McMenamin JB, Shakelford GD, Volpe JJ. Outcome of neonatal intraventricular hemorrhage with periventricular echodense lesions. Ann Neurol 1984;15(3):285-90.

OUTPATIENT MANAGEMENT OF CHILDHOOD DIABETES: EXPERIENCE OF A PEDIATRIC DIABETES CLINIC AT KING KHALID UNIVERSITY HOSPITAL, RIYADH

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يصف هذا المقال خبرة السنوات الأربع الأولى في عيادة للأطفال المصابين بالسكري، أنشئت في سنة ١٩٨٣م ووضعت تحت اشراف فريق. سجل ستون طفلا دون سن الثانية عشرة خلال هذه الفترة، ٣٤ صبيا و٢٦ بنتا، وتلقى جميع المرضى ووالديهم برنامجا تعليميًا في المراجعة الأولى وبعدها. حتى الأميين من الآباء والأمهات تلقوا تدريبا في مرحلة مبكرة. غير أن اختلال توافر الأنسولين و/أو محاقن الأنسولين سبب ارباكا للمرضى. كانت المفاهيم الخاطئة عن الغذاء شائعة وتطبيق الارشادات الغذائية أصعب مما هو عليه في الأماكن الأخرى، وبالتالي كان ٣١ر١٪ تقريبا من الأطفال غير ملتزمين بأي حمية. تم تدريب ٩٤٪ تقريبا من المرضى على مراقبة غلوكوز في منازلهم. وبعد اجراء تحليل لخمسة وأربعين مريضا اتضح أن ٢٦ (٦١ر٩٪) كانوا يقومون بالمراقبة بانتظام و١٢ (٢٨ر٦٪) بغير انتظام و٤ (٩ر٥٪) توقفوا عن القيام بها تماما. غير أنه لم يحدث التوقف عن فحص البول لدى أي من المرضى. وكان متوسط الهيموجلوبين المرتبط بالغليكوزيل لدى المرضى ١١ر٥٪. وقد ساعد برنامج تدريب الآباء ونظام الاتصال الهاتفي على تقليل الحاجة إلى دخول المستشفى لدى الأطفال. وبناء على هذه الخبرة تمت صياغة مجموعة توصيات لمساعدة الأطفال وآبائهم في تدبير سكري الطفولة.

This article describes the first 4 years' experience of a clinic for children with diabetes which was established in 1983 and was run by a team. Sixty children below 12 years of age were registered during this period, 34 boys and 26 girls. All the patients and their parents were given an educational program at first contact and thereafter, and even the illiterate parents were trained early. Variations in the availability of insulins and/or insulin syringes created confusion among parents. Dietary misconceptions were common, and dietary instructions were more difficult to impose than elsewhere; as a result, almost 31.1% of children were on a free diet. Almost 94% of patients were trained on home blood glucose monitoring. Out of 45 patients analyzed, 26 (61.9%) were doing it regularly and 12 (28.6%) irregularly; four (9.5%) had stopped it completely. In none of the patients was urine testing stopped completely. The mean glycosated hemoglobin in the patients was 11.5%. Parents' training and a phone call system helped prevent hospitalization of children. On the basis of this experience, a series of recommendations have been formulated to assist children and their parents in the management of childhood diabetes.

Diabetes mellitus in childhood has been considered rare in African[1,2] and Asian[3-5] populations, although little published information is available. The subject of diabetes mellitus in Saudi Arabia has been recently reviewed.[6]

In developing countries, management of diabetic children may impose different sorts of problems in view of the high illiteracy rate, economic difficulties, different dietary habits, insulin availability, food and insulin storage problems, difficulty of follow-up, and lack of proper records. Saudi Arabia is a unique country in the Third

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World in view of its excellent economic status, relatively low literacy rate, particularly among mothers, in addition to the cultural and religious background which might influence the management of diabetes.

In this paper, we describe our experience in a pediatric diabetes clinic which was established in King Khalid University Hospital in Riyadh and highlights some of the practical problems related to the routine management of children with diabetes in the Kingdom. Some recommendations are made based on this experience.

Subjects and Methods

The Diabetes Clinic

The pediatric diabetes clinic was established in July 1983. It was initially run by the author with a clinic nurse, and gradually, a team composed of an Arabic- and English-speaking diabetes nurse educator who was trained by us, a social worker, a dietitian, and a clinical pharmacist was established The clinic was conducted once weekly, and usually six to eight patients were seen per session.

Clinic Population

Records of all children registered in the pediatric diabetic clinic between July 1983 and August 1987 were analyzed. Parents of 45 patients and their elder children who attended the clinic over the most recent 3 months were further interviewed directly by the author, and information on current status of urine testing, home blood glucose monitoring, and diet was collected in addition to the data obtained from the records. Data on age, sex, nationality, and age of onset of diabetes were obtained. Based on the father's education, father's occupation, and family's housing, the patients were classified into three social classes: upper, middle, and lower, as designated by the College of Medicine's Department of Community Medicine.

Education

All the newly diagnosed cases were initially admitted to the hospital with their mothers for stabilization and education on all aspects of diabetes and its management for a period of 5 to 10 days. We depended mostly on practical demonstrations and face-to-face education. We relied on simple diagrams and drawings for education of illiterate parents. Our goal was to attain a patient and parental level of knowledge which would ensure independence, so as to permit timely discharge from the hospital.

Discharge and Follow-up

On discharge, each patient was provided with a labeled card containing the patient's hospital number, insulin dosages, and hospital phone numbers. Parents were told that they were free to call the team members at any time, 24 hours a day.

Follow-up was done weekly for the first month, except for those coming from outside Riyadh, then every 2 weeks for 1 month, monthly for 2 months, and every 2 to 3 months thereafter. After the first few months of stabilization, those coming from far distances were seen every 4 to 6 months, and arrangements were made with the nearest local pediatrician to follow them during that period. Those who defaulted their clinic appointments were phoned, and new appointments were fixed.

Clinic Visits

On each clinic visit, the patients and their families were seen by various members of the team individually or as a group for education and review of the management, in addition to physical examination including weight, height, thyroid size, dental hygiene, liver size, and injection sites. The HbA_1 determination was done every 2 months. Urinalysis was done on each clinic visit, but not blood glucose. The urine and blood testing records were checked. We insisted that parents bring their insulin vials, syringes, and monitoring devices for double-checking and educational purposes. Insulin and insulin syringes were mostly provided free of charge by the hospital. Urine and blood testing strips were mostly bought by the parents. Low-income patients were given support by our social services and patient relationship departments.

Insulin Therapy

All newly diagnosed cases and those who developed reactions to beef insulin were started on human insulin. Patients who were already on beef insulin were put on monocomponent beef insulin. For religious reasons, none of the patients received pork insulin. Insulin doses of 100 units/mL as well as 100-unit syringes were used. Low-dose 0.5-mL 27-gauge syringes, when available, were used for young children. Illiterate parents were taught by marks (lines) on the syringes as well as by units and colored drawings showing the insulin dosages provided in addition to labeling of the syringes. Over the last year, patients were encouraged to reuse the syringes without sterilization until the needles became blunt.

Parents and children over 8 years old were trained to give injections. We tried to put most of the children on twice daily injections of a mixture of NPH and regular insulin. Children who fasted during Ramadan were advised to have their morning dose before sunset and either to omit or to have a small dose of regular insulin (depending on blood glucose testing) at "sahoor" time (around 3 to 4 AM) when the last meal is taken and fasting starts.

Diet

We followed the basic principles of dietary therapy for children with diabetes.[7,8] For many families, we gave simple, practical instructions with food items being modified according to the locally used food rather than insisting on weight and calorie language.

School and Diabetes

Letters explaining the nature of the disease and advice on handling these children at school were sent to each child's school. Teachers were encouraged to contact us with any questions.

Home Blood Glucose Monitoring

We tried to train most of our patients on home blood glucose monitoring. For practical reasons, including cost and availability of strips, Glucometer II ames and Reflolux II BM meter and Haemoglukotest strips were used. For the first 2 to 4 weeks after discharge, we advised blood testing four times per day: before breakfast, lunch, supper, and bedtime, as well as when the child felt unwell. Thereafter, it was done on alternate days and then twice per week. We aimed at a blood glucose level of 4.4 to 10.0 mmol/L as a reasonable compromise for children. Parents were allowed to adjust the insulin dose by 10% to 20% of the total if the blood glucose level was persistently higher or lower during sick days. However, parents were told to call us if they had any doubts about the correct dose. Parents were also advised to give an extra dose of regular insulin (0.1 unit/kg or prefixed as marks for illiterate parents) if there was a party (azzimmas) where a large amount of food is usually consumed.

Urine Testing

All the families were trained on urine testing. Simple strips containing glucose and ketone, needing dry wiping, then washing with water (Ketodiastix-ames; Ketodiabeur-BM) were preferred. Those on regular blood glucose monitoring were advised to check urine daily only if blood glucose was high (> 13.3 mmol/L); otherwise, it was done two to four times per day on the days when blood glucose was not measured. Low-income families and those who ran short of strips were advised to divide the strips with scissors.

Glycosated Hemoglobin

The glycosated hemoglobin (HbA_1) was measured in all our patients every 2 to 3 months. Glytrac kits were used for this test. Our laboratory reference range was 660 to 880 mmol/L. As hemoglobinopathies and other hemolytic anemias which influence the level of HbA_1 are common in Saudi Arabia, we tried to exclude them in our patients.

Complications

All our patients and their families were trained to recognize and manage symptoms of hypoglycemia. We did not induce hypoglycemia during the child's stay in the hospital. Glucagon was provided to some of the parents. Parents were also trained to handle mild ketosis at home. They were encouraged to phone us otherwise. All the children were seen annually by the ophthalmologist.

Results

Clinic Population

A total of 60 children were registered in the clinic up to August 1987. Twenty-five children were newly diagnosed in our hospital and 35 were referred from other hospitals; 33 (55.0%) presented with ketoacidosis at onset. Thirty-four (56.7%) of the group were male and 26 (43.3%) female. Forty-one (68.3%) were Saudis and 19 (31.7%) non-Saudis. The latter included Palestinians, Egyptians, Sudanese, Jordanians, Yemenis, Pakistanis, and Indians. Their ages varied from 6 months to 12 years. According to the hospital policy, children over 12 years were gradually referred to the adult physicians.

Social classification showed that 15 (25.0%) were from upper, 32 (53.3%) from middle, and 13 (21.7%) from lower social class. Forty-six percent of the mothers were illiterate. Only six (10.0%) of the patients had no telephones at home. Two of these were bedouins living in the real desert. These latter two also had no refrigerators at home. They were advised to store some insulin near the water pot away from light and stock the rest in the nearest health center.

Education

Though we have not yet properly evaluated our educational program, we were very much impressed with the improvement in the parents' performance, including the illiterate mothers. Most parents preferred face-to-face education and practical demonstrations rather than books and written instructions. As most of the children were looked after by the mothers, we have found that they were more frank and more at ease with the female educator. Most of the instructions related to drugs and equipment provided by the companies were written in English and thus needed translation to Arabic by the clinic team.

Insulin Therapy

Forty-eight percent of our cases were on human insulin and 52% on monocomponent beef insulin, with 26.7% on once-daily and 73.3% on twice-daily injections of a mixture of regular and NPH insulin. Three children were taking their single daily injections before lunch (2 PM), as they would refuse to go to school if their injections were given in the morning. Eight fasted during Ramadan, and no problems were encountered with the insulin regimen as described earlier. Out of 60 patients, 50 were usually injected by their mothers, eight injected themselves, one was done by the father, and one by a hired nurse. Over the last year, about 72% of the patients were reusing the syringes from two to four times without sterilization, and no infections were encountered. The commonest reason for changing the syringe was needle-blunting.

Using 40 units/mL and 80 units/mL of insulin with 100-unit syringes was one of the commonest problems which we observed among the newly referred cases or among parents, particularly those coming from outside Riyadh, who purchased syringes and insulin from the market when they ran short of them.

Diet

Out of 45 children on whom the dietary history was closely reviewed, 17 (37.8%) were compliant with their diet, 14 (31.1%) admitted taking soft drinks, and 14 (31.1%) were having an almost free diet. One third of the parents strongly believed that honey and dates could be freely eaten by the diabetics. Many parents attributed the difficulties of diet control to sociocultural reasons and living with other children in the same house. Unlike eating habits elsewhere, many children did not like having breakfast at 6 or 7 AM; rather, it was taken at 9 or 10 AM in the school. We were therefore adjusting the insulin dosage accordingly by giving smaller doses of regular insulin in the morning.

School and Diabetes

The communication which we attempted to make with the schools was welcomed and solved many problems. Some school authorities, particularly the kindergartens, were initially reluctant to accept diabetic children. Some of the parents were also trying to avoid disclosing the problem to the school authorities. We managed to reinstate two of our patients who left school for these reasons.

Home Blood Glucose Monitoring

Nineteen (42.2%) out of 45 patients were trained on using blood glucose meters, 23 (51.1%) on visual methods, and only three (6.7%) were not trained for social reasons or reluctance to accept blood glucose monitoring. Most parents preferred to have their meters adjusted in mg rather than in mmol. When we reviewed the 42 patients who were trained, 26 (61.9%) were still monitoring fairly regularly, 12 (28.6%) were very irregular, and four (9.5%) had stopped it completely. Patients who were trained and started on monitoring at the onset of the disease were the most regular ones. Some of the irregularities resulted from difficulties encountered with maintenance of the meters or availability of the strips in the market, particularly when meters were purchased abroad. The monitoring was done by the parents, usually the mother, in 36 of the 42 patients (85.7%); five children (11.9%) did their own monitoring, and in one patient (2.4%), a nurse was hired for this purpose.

Urine Testing

Out of 45 patients, urine testing was done by parents in 35 (77.8%) and by children in 10 (22.2%); 37 (82.2%) did it regularly and eight (17.8%) irregularly. None of them stopped urine testing. Four of the patients were dividing the strips with scissors and found no problems with it. Their results on double checking in the clinic were fairly comparable. Combur-8 and other multitest strips were found to be very confusing to the parents. Variations in the meaning of cross marks (+ or ++) were observed among different strips available in the market.

Glycosated Hemoglobin

The mean HbA_1 in our patients was 11.5% (range, 6.5% to 16.2%). Only one patient was found to have combined G6PD deficiency and HbAS.

Complications

Over the last 4 years, we admitted only two of our patients with symptomatic hypoglycemia, and four patients were readmitted with diabetic ketoacidosis. Two of the latter needed repeated admissions for social reasons. All the rest of the patients were managed by the parents at home, and we have managed many cases with mild ketosis, who might otherwise have needed a clinic visit or hospitalization, by advising the parents over the phone.

The overall growth pattern on follow-up was within normal limits, except one child who developed gross hepatomegaly and relatively poor growth before we realized that the parents were using a different syringe and giving half the recommended dose of insulin.

No ophthalmic or renal complications were encountered among the patients.

Discussion

Diabetes mellitus in children, like other chronic diseases, needs provision of a comprehensive, coordinated, and continuous service.[9] This is best provided by teamwork. The core members of the team, in addition to the patient and his or her family, are the pediatrician, diabetes nurse educator, dietitian, pharmacist, social worker, and psychologist if available.[9,10]

In Saudi Arabia, as in many developing countries, the cut-off age for children is around 12 years of age, and there are no special services for adolescents. It is preferable that pediatricians and adult physicians with an interest in diabetes conduct combined clinics to look after this group of children who can then be weaned gradually to the adult physicians. In many countries, including Saudi Arabia, it might be difficult to get enough trained team members and laboratory facilities to run clinics for children with diabetes in each hospital. Therefore, in order to improve the service and experience, we suggest that fully staffed referral clinics for children with diabetes should be created in each region. General practitioners should be trained in diagnosis and management of children with diabetes, particularly their emergency problems. Thereafter, these cases should be referred to these regional clinics. Well-trained parents, in our experience, can easily handle their children otherwise.

It is emphasized that 90% of successful diabetes management involves skillful education by health professionals and accurate learning by the patient.[9,10] The rest depends on advice from the physician. The diabetes educator is an indispensable member of the team. In Saudi Arabia, we believe that the most suitable educator is a local female who speaks both Arabic and English. Either nurses or perhaps graduates of the College of Applied Medical Sciences could be trained for that purpose.

The answer to problems arising from the availability of various insulin syringes and preparations is for the Ministry of Health to take active steps to standardize them. One would suggest 100 unit/mL human or monocomponent beef insulin and 100 unit/mL low-dose of 0.5-mL 27-gauge and 1-mL syringes.

The subject of diet and diabetes in children has recently been extensively reviewed.[7,8] The major problems encountered in Saudi Arabia are noncompliance, cultural beliefs, and misconceptions. This is similar to the experiences in other Gulf countries.[11] In a country where extended rather than nuclear families exist and where more than one family lives in one house-complex, it becomes a difficult task for the parents to control their children. Therefore, one has to be realistic and give simple dietary instructions and individualize the dietary advice depending on the knowledge and motivation of the family. As shown in this study, in spite of repeated educational sessions, almost 30% of children continued having an almost free diet.

The subject of home blood glucose monitoring and its superiority to urine testing has been reviewed elsewhere.[12-16] Among the practical problems with home blood glucose monitoring are compliance and the cost. Initial intensive education followed by repeated review sessions tends to improve compliance,[16] as has been shown in our cases where almost 60% continued doing it regularly. Parents should avoid purchasing meters which do not have agents for maintenance or easily available strips in the Kingdom.

The limitations of urine testing have been discussed elsewhere.[13,15] As shown in this study, one of the major problems encountered in the Kingdom is variation in the available strips. We therefore recommend that the types of strips available in the market should be standardized, if possible, preferably to simple strips for glucose and ketone testing only.

The value of assaying the HbA_1 level in diabetic patients has been emphasized.[17-19] One North American clinic has reported that the mean HbA_1 concentration in their clinic was 11.8%.[20] We had a comparable figure of 11.5% in our clinic. In Saudi Arabia, we recommend that this test be made available at least at regional levels.

The duration of diabetes and follow-up in our patients was too short to expect or draw conclusions on chronic complications of diabetes.

Conclusion

In conclusion we believe that children with diabetes should be seen by pediatricians. Special pediatric diabetic clinics with trained team members should be set up in each city or region. General practitioners should also be trained to handle these children. Adolescents should be seen in cooperation with adult physicians. More effort should be put into education of the patients and their families to make them self-reliant and independent. Treatment and monitoring facilities should be made easily available. Insulin strengths and syringes should be standardized throughout the Kingdom to minimize confusion. Doctors should be realistic in the dietary education of the families. Studies to define the magnitude of childhood diabetes and to give guidelines on management based on local experience are recommended.

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References

1. Alberti KGMM. World aspects of diabetes. Diabetic Med 1986;3:103-5.
2. Lester FT. Childhood diabetes in Ethiopians. Diabetic Med 1986;3:278-80.
3. Patel JC, Ohirawami MK, Kabun AN. In: Patel JC, Tawalker NG, eds. Diabetes mellitus in the tropics. Bombay: Diabetes Association of India, 1968:69-73.
4. Tsai SH. Clinical features of diabetes in Taiwan. In: Baba S, Goto I, Fukui I, eds. Diabetes mellitus in Asia. Amsterdam: Excerpta Medica, 1976:69-73.
5. Samanta A, Burden AC, Jones GR, et al. Prevalence of insulin-dependent diabetes mellitus in Asian children. Diabetic Med 1987;4:65-7.
6. Sebai ZA. Diabetes mellitus in Saudi Arabia. Postgrad Doctor Middle East 1987;10(10):582-6.
7. Brink SJ. Pediatric, adolescent, and young-adult nutrition issues in IDDM. Diabetes Care 1988;11(2):192-200.
8. American Diabetes Association. Position statement: nutritional recommendations and principles for individual with diabetes mellitus: 1986. Diabetes Care 1987;10(1):126-32.
9. Rosenbloom AL. Primary and subspecialty care of diabetes mellitus in children and youth. Pediatr Clin North Am 1984;31(1):107-17.
10. Sperling MA. Outpatient management of diabetes mellitus. Pediatr Clin North Am 1987;34(4):919-34.
11. Bancroft-Livingstone M. Diabetes in the gulf: the future epidemic. Postgrad Doctor Middle East, November 1984:654-66.
12. Brownlee M. Achieving better blood glucose control. Drug Therapy 1981:59-70.
13. Brouhard BH. Control and monitoring for the child with insulin-dependent diabetes mellitus. Am J Dis Child 1983;137(8):787-94.
14. Price DA. Diabetes: II. Strict glycaemic control (editorial). Arch Dis Child 1984;59(9):810-2.
15. Unger RH. Meticulous control of diabetes: benefits, risks, and precautions. Diabetes 1982;31(6 pt 1):479-83.
16. McDonald MJ. Personal glucose testing in children. Primary Care 1983;10(4):565-80.
17. Goldstein DE. Understanding GHb assays: a guided tour for the clinicians. Clinical Diabetes Jan-Feb 1986;4(1):1-11.
18. Daneman D, Wolfson D, Becker DJ, Drash AL. Factors affecting glycosated hemoglobin values in children with insulin-dependent diabetes. J Pediatr 1981;99(6):847-53.
19. Wright AD, Northam BE. Glycosylated haemoglobin in diabetes mellitus. Postgrad Doctor Middle East, March 1982:118-22.
20. Ellis D, Becker DJ, Daneman D, et al. Proteinuria in children with insulin-dependent diabetes: relationship to duration of disease, metabolic control, and retinal changes. J Pediatr 1983;102(5):673-80.

NUTRITIONAL PROFILE OF SAUDI PRIMARY SCHOOLGIRLS IN AN URBAN REGION

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أجري مسح تناول القياسات البشرية لمائتين وخمس وثمانين طالبة ابتدائية سعودية من الحضر في منطقة الثقبة، بالخبر، في المنطقة الشرقية للمملكة العربية السعودية. كما أجريت تقديرات للهيموجلوبين وتحليل مخبري لاستقصاء البيوض والكييسات في البراز. وعند مقارنة النتائج بالمقاييس المعتمدة لدى المركز القومي الأميركي للاحصاءات الصحية جاءت «قياسات الطول بالنسبة إلى السن» دون المتوسط، وتراوحت بين ١٠ و ٢٥ بالمئة، باستثناء الطالبات في سن السادسة اللواتي لم يظهرن توقفا عن النمو. هذه السمة تستبعد احتمال حدوث سوء تغذية شديد قبل الولادة وفي سن الرضاع. أما نتائج «قياسات الوزن بالنسبة إلى الطول» فقد أظهرت ميلا نحو فرط التغذية، مما يجعلنا نميل إلى الاعتقاد بوجود عامل وراثي، اكثر منه غذائي، مسئول عن توقف النمو لدى الأطفال الأكبر سنًا. كما أظهرت النتائج اصابة ٢٦٫٤٪ من هؤلاء الطالبات بفقر الدم، و ٩٫٢٪ بطفيلي واحد أو أكثر، وكان فقر الدم شائعا أيضًا لدى المصابات بالإنتان الطفيلي.

Two hundred eighty-five primary schoolgirls from the urban area of Thugba, Al-Khobar, in the Eastern Province of Saudi Arabia were examined anthropometrically. Hemoglobin estimations and laboratory stool analysis for ova and cysts were also performed. When compared to the standards of the US National Center for Health Statistics, the height-for-age measurements were below the median, lying between the 10th and 25th percentiles except in the 6-year-olds, who showed no stunting. This feature excludes the possibility of severe malnutrition in the prenatal period and infancy. Weight-for-height performance showed a trend toward overnutrition. We are thus inclined to believe that there is a genetic rather than nutritional component for stunting in the older children. Of the study group, 26.4% had anemia, and 9.2% were infested with one parasite or more, and anemia was common in those harboring infestations.

Whereas most studies on nutritional status in Saudi Arabia have been conducted on preschool children,[1-5] data from urban-based samples and particularly the school age group are scarce. With 72% of the population urbanized in the Kingdom, according to 1985 data,[6] there is a need to investigate the health situation in cities and towns for a more realistic picture of the country. Moreover, schoolchildren are in a phase when growth and development are continuing, and though they are not in the precarious state of health as preschool children, they are often malnourished and suffer from a variety of parasitic and infectious diseases. They are also in an impressionable stage. Economically and logically, school age is the right time and place for health and nutrition education to show long-term results.

With these facts in view, the present study was conducted in the urban area of Thugba (Al-Khobar, Eastern Province of Saudi Arabia) to evaluate the nutritional profile of female primary schoolchildren at the ages of 6 through 12 years and to conduct need-oriented health education

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sessions. We felt such data would eventually provide a basis for the planning of a broader based study of Saudi schoolchildren.

The present research formed a major part of the requirements for a field training program of undergraduate medical students (level IV) in community medicine.

Sampling and Methods

Thugba residents could be largely classified as belonging to a middle socioeconomic level. Our intention was to investigate the nutritional profile of schoolchildren representative of this community; hence, we selected only public schools of that area, excluding private institutions. Again, since female medical students were involved in this research, only schools for girls were included in the study sample. There were 10 such public primary level schools with a total female student population of 1700. Two schools out of 10 were selected by random technique. An effort was made to examine all the children of the first school; however, due to time constraints in the training period of medical undergraduates, we had to limit our sample size in the second school. To avoid any bias in the selection of children from the latter school, we chose one section randomly out of the two for each grade level and investigated all the children from that section.

The total number of examined children from both schools was 285 (approximately 17% of the total female primary schoolchildren). The present research was designed as a cross-sectional study and was completed in a 2-week period in February 1987.

To evaluate the nutritional status of the children, the following methods were adopted: (1) anthropometric measurements for height and weight and (2) hemoglobin estimations. Weight was noted on a lever balance (single beam clinic scales) to the nearest 0.1 kg. Care was taken that children were not wearing heavy woolen clothes while being weighed. The scales were checked for accuracy before starting the survey and then rechecked periodically. Height was measured without shoes on a stadiometer, and readings were adjusted to the nearest 0.1 cm.

The growth performance of the children was compared with the new NCHS standards[7] which have been favorably recommended by Waterlow et al.[8] Their suggestions on age groupings were also followed. A take-home questionnaire completed by parents verified the accuracy of the children's ages. We focused our analysis on height for age and on weight for height, which are considered as primary indicators of nutritional status in children by the FAO/UNICEF/WHO Expert Committee on Nutritional Surveillance.[9]

Several studies have reported the significant prevalence of anemia in Saudi children.[1,2,10] We, therefore, made an effort to estimate the hemoglobin level, which is also an important index of health and nutritional status. Hemoglobin estimations were made with the help of Drabkin's reagent (potassium ferricyanide and potassium cyanide). The mixed sample of blood and reagent in vitro was measured for its color intensity against a standard solution of cyanmethemoglobin.

Microscopic examination of stools for ova and cyst on sediments following centrifugation technique was also performed for most of the children (84.2%). The remaining students did not turn in their stool samples.

Results

The age distribution of the children as well as their mean weights and mean heights are presented in Table 1. In comparison with the NCHS standards, the average heights of Saudi girls fell between the 10th and the 25th percentiles except in the 6-year-olds whose mean height was above the 25th percentile and indicated no stunting. Average weight performance was better than height in all age groups. Mean weights according to age fell between the 25th and the 50th percentiles of the NCHS standards. The relative position

TABLE 1. *Mean heights and weights of children according to age.*

Age (y)	Total no.	Mean height(SD)* (cm)	Mean weight(SD)* (kg)
6– 6.99	17	112.60(5.14)	19.49(3.50)
7– 7.99	51	116.25(6.15)	21.65(4.70)
8– 8.99	68	121.08(6.26)	23.94(6.32)
9– 9.99	46	124.43(6.82)	26.88(10.33)
10–10.99	54	130.85(6.01)	31.17(9.11)
11–11.99	37	137.48(5.18)	33.21(6.50)
12–12.99	12	143.50(7.74)	36.55(6.70)

*The figures in parentheses are standard deviations.

of the mean heights and mean weights of our study with that of the reference population is seen in Figures 1 and 2. As age increased, the deviation of Saudi mean weights from the standard became greater (Figure 2).

Table 2 summarizes the distribution of weights for heights of the study population according to standard percentiles in different age groups. At all ages, about 60% of the students were above the reference median except in the 6-year-old group, where 15% more children than in the reference population fell below the 50th percentile. In the latter category, most of them weighed between the 40th and the 50th percentiles (no wasting). In other age groups, a considerable excess of children were found in the 90th to 100th percentiles, showing a trend toward overnutrition.

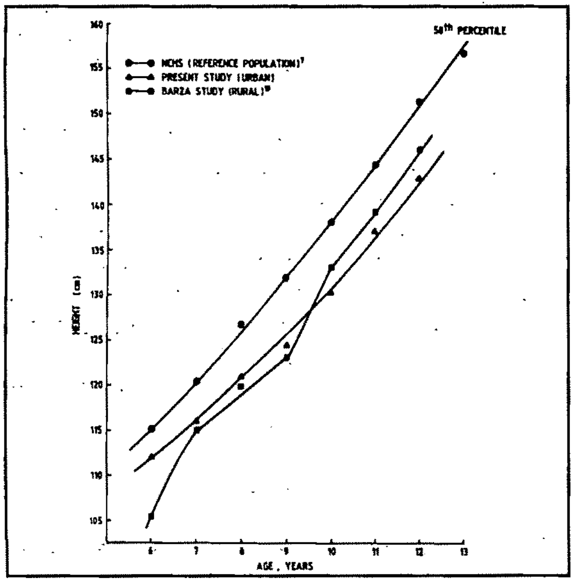

FIGURE 1. Heights for age of Saudi primary schoolchildren compared to other studies.

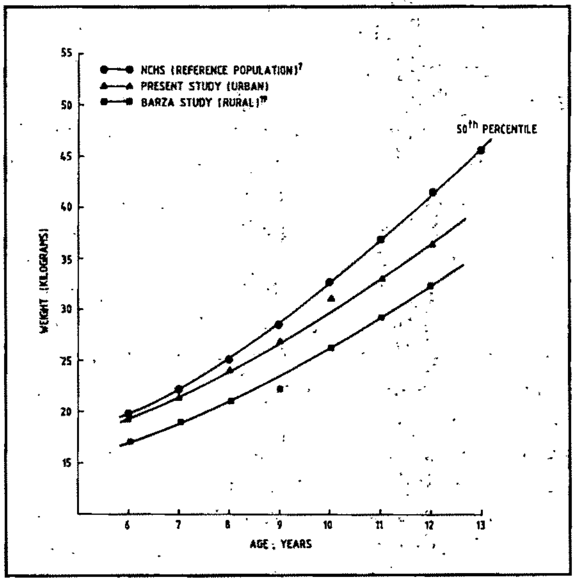

FIGURE 2. Weights for age of Saudi primary schoolchildren compared to other studies.

TABLE 2. *Distribution of weights for heights of Saudi primary schoolgirls according to percentiles of NCHS standards.**

Percentile weight for height	Age(y)							
	6–6.99	7–7.99	8–8.99	9–9.99	10–10.99	11–11.99	12–12.99	Total
0–9.99	1(5.9)	3(5.9)	4(5.9)	4(8.7)	0	0	0	12(4.2)
10–19.9	1(5.9)	5(9.8)	3(4.4)	0	2(3.7)	4(10.8)	1(8.3)	16(5.6)
20–29.9	3(17.6)	7(13.7)	3(4.4)	4(8.7)	8(14.8)	6(16.2)	2(16.7)	33(11.6)
30–39.9	2(11.7)	3(5.9)	8(11.8)	6(13.0)	6(11.1)	4(10.8)	2(16.7)	31(10.9)
40–49.9	4(23.5)	2(3.9)	9(13.2)	4(8.7)	5(9.3)	2(5.4)	0	26(9.1)
Total < 50	11(64.7)	20(39.2)	27(39.7)	18(39.1)	21(38.9)	16(43.2)	5(41.7)	118(41.4)
50–59.9	0	3(5.9)	4(5.9)	2(4.3)	1(1.9)	3(8.1)	2(16.7)	15(5.3)
60–69.9	1(5.9)	4(7.8)	10(14.7)	4(8.7)	4(7.4)	3(8.1)	0	26(9.1)
70–79.9	1(5.9)	6(11.8)	3(4.4)	1(2.2)	7(13.0)	2(5.4)	1(8.3)	21(7.4)
80–89.9	1(5.9)	4(7.8)	11(16.2)	6(13.0)	5(9.3)	5(13.5)	1(8.3)	33(11.6)
90–100	3(17.6)	14(27.5)	13(19.1)	15(32.6)	16(29.6)	8(21.6)	3(25.0)	72(25.3)
Total ≥ 50	6(35.3)	31(60.8)	41(60.3)	28(60.9)	33(61.1)	21(56.8)	7(58.3)	167(58.6)
Total	17	51	68	46	54	37	12	285

*The figures in parentheses are percentages.

We then analyzed height for age and weight for height of the children in categories which are multiples of standard deviations away from the standard mean (Table 3). The distribution of height for age in the present study shifted to the left of the normal distribution of the reference population with 64.5% of the children below -1 SD (standard deviation) as compared to the expected value of 15.87%. Of the 285 children, 75 (26.3%) had a height which was ≤ -2 SD of the reference median, indicating stunting. On the other hand, when weight-for-height measurements were considered, only five of the 285 children (1.7%) were wasted (≤ -2 SD of the reference median), there being more (14.4%) who were significantly overnourished (≥ 2 SD of reference median).

Table 4 represents a classification of malnutrition proposed by Waterlow et al[8] in which the independent distributions of height for age and weight for height are combined in a cross tabulation. When ≤ -2 SD of the reference median is the cutoff point for undernutrition in relation to both these indicators, only one child (0.3%) was found to be both stunted and wasted. Conversely, when high weight for height (≥ 1 SD of the reference median) was considered as overnutrition,[11] then a large number of children, i.e., 77 (27%), fell in this category; 41 of these children (14.4%) could have been considered obese (weight for height ≥ 2 SD), and the remaining 36 (12.8%) appeared to be overfed but not necessarily obese (1 to 1.99 SD).

TABLE 3. *Distribution of height for age and weight for height of Saudi primary schoolgirls based on values of standard deviations above and below the NCHS medians.*

Standard deviation of NCHS median	Height for age No.(%)	Weight for height No.(%)	Expected values in % (reference standards)
≤-2 SD	75(26.3)	5(1.7)	2.27
-1.99 to -1 SD	109(38.2)	44(15.4)	13.60
-0.99 to 0.99 SD	99(34.7)	159(55.8)	68.28
1 to 1.99 SD	2(0.7)	36(12.6)	13.60
≥2 SD	0	41(14.4)	2.27
Total	285*	285*	

*Percentages may not total 100% due to rounding.

Of the 285 children, 242 (84.9%) cooperated for hemoglobin estimations. Table 5 presents the mean level of hemoglobin and prevalence of anemia according to age. Sixty-four of the 242 children (26.4%) had hemoglobin levels below 110 g/L, indicating anemia.[12] A lesser proportion of students in the age groups of 10 and 11 years were anemic as compared to those in the other age levels.

The response rate for stool tests was 84.2% (240/285). Microscopic examination of stool by the concentration technique showed a variety of parasites including *Giardia lamblia* (2.5%), *Entamoeba histolytica* (2.1%), *Enterobius vermicularis* (1.6%), *Hymenolepis nana* (1.2%), and *Trichuris trichiuria* (0.8%). Twenty-two girls (9.2%) had infestation by one or more parasite. Such infections are generally a common cause of iron-deficiency anemia and malnutrition in children.[12] In our study, those with parasites had a significantly higher (38.4%) prevalence of anemia as

TABLE 4. *Cross tabulation of weight for height and height for age based on the values of standard deviation above and below the NCHS medians.*

Weight for height	Height for age*					
Standard deviation of NCHS median	≤-2 SD	-1.99 to -1.00 SD	-0.99 to 0.99 SD	1.00 to 1.99 SD	≥2 SD	Total
≤-2 SD	1(0.3)	3(1.1)	1(0.3)	0	0	5(1.7)
-1.99 to -1 SD	18(6.3)	12(4.2)	14(4.9)	0	0	44(15.4)
-0.99 to 0.99 SD	43(15.1)	69(24.2)	47(16.5)	0	0	159(55.8)
1 to 1.99 SD	7(2.5)	11(3.9)	17(6.0)	1(0.4)	0	36(12.6)
≥SD	6(2.1)	14(4.9)	20(7.0)	1(0.4)	0	41(14.4)
Total*	75(26.3)	109(38.2)	99(34.7)	2(0.7)	0	285

*The figures in parentheses are percentages. Percentages may not total 100% due to rounding.

TABLE 5. *Mean hemoglobin level and prevalence of anemia according to age.*

Age (y)	No.	Mean hemoglobin (g/L)*	Hemoglobin ≤110 g/L No.(%)
6–6.99	15	116.8(9.9)	4(26.7)
7–7.99	43	115.3(7.6)	12(27.9)
8–8.99	54	110.6(10.6)	24(44.4)
9–9.99	35	114.3(9.5)	11(31.4)
10–10.99	50	120.8(9.8)	6(12.0)
11–11.99	33	122.2(8.9)	2(6.1)
12–12.99	12	115.0(11.5)	5(41.7)
Total	242	118.0(9.7)	64(26.4)

*The figures in parentheses are standard deviations.

compared to those (21.8%) without infestations ($\chi^2 = 10.84, P < 0.001$). However, only 11.6% of the anemic subjects had parasites, indicating the likelihood of other important factors as causes of anemia.

Discussion

Nutritional Status

Data on the nutritional status of Saudi schoolchildren are limited. The present study, though of a small sample size, provides an appraisal of the state of nutrition of primary schoolgirls belonging to the middle social class of an urban population. More extensive studies are required to establish local standards for anthropometric measurements, which are hitherto lacking in the Kingdom.

Height for age, which is considered an indicator of past nutritional status,[8] was found to be largely below the reference standard in the study population. However, an interesting feature observed was that the 6-year-olds did not show stunting. This finding excludes the probability of severe or prolonged malnutrition in the critical growth periods of intrauterine life of infancy.[13] Habicht et al[14] have demonstrated that well-fed persons of various ethnic groups tend to approximate to standard levels in infancy and the preschool period. Our observations, therefore, suggest a genetic rather than nutritional component for stunting in the later years of life. Moreover, when shortness of height upon weight is estimated and only the degree of underweight or overweight is measured, there are more children with high weight for height than expected by reference population standards (Table 3). In the absence of any recent nutritional intervention program in this community, these findings further highlight a genetic control on height and thus question the validity of comparisons with international standards. In such situations, Waterlow et al's[8] suggestion to set a target height at 95% of the reference height seems appropriate.

The cross-tabulated observations combining both height for age and weight for height as indicators of malnutrition have been useful in interpreting the nutritional status of children in the present study. Whereas only one child (0.3%) was both stunted and wasted, 41 children (14.4%) were possibly obese, and 36 (12.8%) were overnourished but not necessarily obese.

Environmental factors have a significant influence on growth, and this has been amply demonstrated in several studies.[15-18] Though the mean heights in our urban-based study were comparable with those of rural Saudi schoolchildren of the same age and sex, the mean weights were significantly better[19] (Figures 1 and 2). Other series from Nigeria,[20] India,[21] and Costa Rica[22] have also reported urban and rural differences in growth.

A prevalence rate of 26.4% for anemia in the present observations was close to 29.2%, but lower than 34% and 36% observed among rural preschoolchildren of Qassim,[23] Turaba[1] and Tamnia,[2] respectively. It was also significantly lower than 39.6% reported from a hospital-based study on anemia in children.[10] This variation is perhaps due to differences in the characteristics of the population studied. A lower prevalence of anemia among the 10- and 11-year-old children of our series cannot be rationally explained in the absence of data on dietetic history and a full range of secondary factors.

The parasite infestation rate in the present study was 9.2%, which is similar to 9.3% reported among Saudi patients attending Riyadh Military Hospital.[24] However, other hospital-based studies on predominantly Saudi populations have observed higher prevalence rates of 18.5%[25] and 25.49%.[26] Community surveys in the Kingdom have also shown a high positivity for infestations in rural preschoolers.[1,2] Information, so far, is lacking on comparative studies of Saudi urban schoolchildren. Among the parasites isolated, *G. lamblia* was the most common one identified in our study. Other series,[1,2,24-26] too, have found this to be an important organism of infestation. In accordance with our expectations, the prevalence of anemia was significantly higher in children with parasites than those without infection, which is similar to that observed by Sebai et al[2] in Tamnia village.

With one fourth of the children anemic in our study, there is a need to explore further the causes of anemia. Studies[27,28] have reported that hemoglobinopathies are highly prevalent in this region, and these may well be an important determinant of the condition. Deworming of the anemic infested children (38.4%) and investigations of abnormal hemoglobins in a follow-up study would help us to identify the major contributory factor for anemia in this community.

Health Education

Observations on the health and nutritional status of children provided important guidelines for the planning of a need-oriented health education program by the undergraduate medical students. It was evident that efforts would have to be focused on a balanced diet that emphasized avoidance of indulgence in carbonated drinks and sweets and noted the importance of safe food and water, personal and environmental hygiene, as well as prevention of anemia. The students prepared health education material during the field training course. They used charts, slides, demonstrations, and role-playing with puppets as their audiovisual aids and techniques in educating the children. At the end of each session, questions were invited from the audience, and discussions encouraged. The health education sessions could only be conducted in the last 2 days of the field program. Benefits resulting from these sessions need to be evaluated subsequently.

Though our study had its limitation of a small sample size, the results are a reflection of the state of health in a rapidly developing country. Severe undernutrition has become rare, and though stunting is reported to be prevalent in several studies,[1-5] wasting is uncommon.[5] In fact, results in our investigation showed a trend toward overnutrition when weight-for-height standards were considered. There is a need for more exploratory studies on the genetic and environmental factors determining nutritional status in the Kingdom.

Needless to say, for the medical students, the school survey, analysis, and interpretation of the data, together with participation in the planning and implementation of health education talks, provided a valuable (though short-term) experience of community-based education.

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References

1. Sebai ZA. The health of the family in a changing Arabia. 3rd ed. Jeddah: Tihama Publications, 1983.
2. Sebai ZA, El-Hazmi MAF, Serenius F. Health profile of preschool children in Tamnia villages, Saudi Arabia. Saudi Med J 1981;2(suppl 1):68-71.
3. Serenius F, Fougerouse D. Health and nutritional status in rural Saudi Arabia. Saudi Med J 1981;2(suppl 1):10-22.
4. Abdulla MA, Sebai ZA, Swailem AR. Health and nutritional status of preschool children. In: Sebai ZA, ed. Community health in Saudi Arabia: a profile of two villages in Qassim region. Saudi Med J, monograph No. 1. Jeddah: Tihama Publications, 1985:11-8.
5. Al-Othaimeen AL, Sawaya WN, Tannous RI, Villanueva BP. A nutrition survey of infants and preschool children in Saudi Arabia. Saudi Med J 1988;9(1):40-8.
6. United Nations Children's Fund. The state of the world's children. New York: Oxford University Press, 1987.
7. National Center for Health Statistics. Growth charts. US Public Health Service, Health Resources Administration, Rockville, MD, 1976, HRA 76-1120, 25, 3.
8. Waterlow JC, Buzina R, Keller W, et al. The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. Bull WHO 1977;55(4):489-98.
9. FAO/UNICEF/WHO. Methodology of nutritional surveillance. WHO Tech Rep Ser 1976;593.
10. McNiel JR. Variations in the response of childhood iron deficiency anemia to oral iron. Blood 1968;31:641-6.
11. World Health Organization. Measuring change in nutritional status. Geneva: WHO, 1983:25-8.
12. Nelson WE, Vaughan VC, McKay RJ, Behrman RE. Nelson textbook of pediatrics. 11th ed. Philadelphia: WB Saunders, 1979;1366-72.
13. Ebrahim GJ. Growth and development of the young infant and the older child. In: Child health in a changing environment. London: Macmillan Press, 1982;38-67.
14. Habicht JP, Martorell R, Yarborough C, et al. Height and weight standards of preschool children: how relevant are ethnic differences in growth potential? Lancet 1974;1:611-4.
15. Navab SW, Hamedi P, Sadre M. Heights and weights of Iranian preschool children in a rural health care network. J Trop Paediatr 1982;28(4):180-6.

16. Goldstein H. Factors influencing the height of seven year old children: results from the National Child Development Study. Hum Biol 1971;43:92-111.
17. Whitehead RG. Infection and the development of kwashiorkor and marasmus in Africa. Am J Clin Nutr 1977;30(8):1281-4.
18. Martorell R, Yarborough C, Yarborough S, Klein RE. The impact of ordinary illnesses on the dietary intakes of malnourished children. Am J Clin Nutr 1980;33(2):345-50.
19. Hammam HM, Kamel LM, Hidayat NM. A health profile of a rural community in the western zone of Saudi Arabia. In: Proceedings of the 4th Saudi medical conference, 27-29 March 1979. Dammam: King Faisal University, 1980.
20. Janes MD. The effect of social class on the physical growth of Nigerian Yoruba children. Bull Int Epidemiol Assoc 1970;20:127-36.
21. Phadke MV, Kulkarni HD. Growth and development in the under-privileged sections in the Bombay area. Proc Nutr Soc India 1971;10:164-76.
22. Villarejos VM, Osborne JA, Payne FJ, et al. Heights and weights of children in urban and rural Costa Rica. J Trop Paediatr 1971;17:31-43.
23. El-Hazmi MAF. Survey of laboratory variables in Qassim children. In: Sebai ZA, ed. Community health in Saudi Arabia. Saudi Med J Monog 1, 1982;19-20.
24. Abu-Saud AS. A survey of the pattern of parasitic infestion in Saudi Arabia. Saudi Med J 1983;4(2):117-22.
25. Mahgoub S, Chowdhury NH, Jamjoom G, et al. A preliminary survey of intestinal pathogenic bacteria and parasites in King Abdulaziz Teaching Hospital, Riyadh. In: Proceedings of the 4th Saudi medical conference, 27-29 March 1979. Dammam: King Faisal University, 1980:272-80.
26. Bolbol AHS, Mahmoud AA. Laboratory and clinical study of intestinal pathogenic parasites among the Riyadh population. Saudi Med J 1984;5(2):159-66.
27. El-Hazmi MAF. Haemoglobin disorders: a pattern for thalassaemia and haemoglobinopathies in Arabia. Acta Haematol 1982;68(1):43-51.
28. Al-Awamy BH, Al-Muzan MI, Al-Turki MT, Serjeant GR. Neonatal screening for sickle cell disease in the Eastern Province of Saudi Arabia. Trans R Soc Trop Med Hyg 1984;78(6):792-4.

HEMODYNAMIC CHANGES AND INTRAVASCULAR HYDRATION STATE IN HEAT STROKE

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أجريت قياسات متسلسلة لدينمية الدم الحادة في ١٣ حاجا (متوسط أعمارهم ٥٥٫٢ ± ٩٫٣ سنة) (انحراف معياري) ممن يعانون من ضربة الشمس (متوسط حرارة المستقيم ٤١٫٣ ± ١ درجة) وأظهرت نمط دوران يتسم بحركية مفرطة مع انخفاض المقاومة المحيطية. كان خمسة من المرضى يعانون من وذمة رئوية مع متوسط منسب القلب ٥،٢٩ ± ٠،٥٦ (انحراف معياري) لتر في الدقيقة لكل مترمربع، والذي يعتبر مرتفعا بشكل طفيف عن متوسط منسب القلب لدى مجموعة المرضى الثمانية الذين لايعانون من الوذمة الرئوية ٤٫٧٦ ± ٠٫٦ (انحراف معياري) لتر في الدقيقة لكل مترمربع. أدى ذلك إلى الاعتقاد بأن هذا المنسب القلبي المرتفع ناجم عن زيادة حمولة الأوعية من السوائل بسبب المعالجة حيث تعذر احتواؤه داخل الأوعية الدموية بسبب عملية التبريد التي رفعت من معدل المقاومة الوعائية المحيطية وانقصت من السعة الوريدية، وأدت إلى اعادة توزيع الدم من الشجرة الوعائية المتوسعة في الجلد إلى الدوران المركزي، تبرز معلوماتنا حقيقة عدم وجود تجفاف ذي أهمية في الحيز في أوعية الدم بالنسبة لمرضى ضربة الشمس. وأفضل علاج لهذه الحالة هو التبريد. ينبغي الأخذ بعين الاعتبار في اجراءات «دعم جهاز القلب والأوعية» تفادي التحميل الزائد بالسوائل بالتسريب الوريدي السريع. بل من الأولى اللجوء إلى الاماهة التدريجية، واعطاء وقت كافٍ لامتلاء الحيز داخل الخلايا عقب التبريد.

Acute and serial hemodynamic measurements in 13 pilgrims (average age, 55.2 ± SD 9.3 years) suffering from heat stroke (average rectal temperature, 41.3 ± 1.0°C) revealed a hyperdynamic circulation pattern and a low total peripheral resistance. Five patients had pulmonary edema with an average cardiac index of 5.29 ± SD 0.56 L/min/m^2, which was slightly higher than the average cardiac index in the group of eight patients without pulmonary edema, 4.76 ± SD 0.6 L/min/m^2. This higher cardiac index was believed to be due to iatrogenic fluid overload which was hard to accommodate intravascularly with the cooling process raising the peripheral vascular resistance, decreasing the venous capacitance, and redistributing the blood from the dilated circulatory bed in the skin to the central circulation. Our data highlight the fact that there is no major intravascular dehydration in heat stroke. The treatment of choice is cooling. The entire process of "supporting the cardiovascular system" should take into consideration avoidance of fluid overload by rapid intravenous fluid administration. Gradual hydration, allowing time for intracellular compartment repletion after cooling, is more appropriate.

Heat stroke is a major health problem during pilgrimage to Makkah (Hajj) in Saudi Arabia. High ambient temperature (up to 48°C), overcrowding, strenuous exercise performing the rituals, and lack of adequate acclimatization are the main contributing factors to heat stroke. Between 1500 and 2000 cases are reported every year during the pilgrimage season. Heat stroke is a medical emergency with a high mortality.[1,2] Serious complications include acute circulatory failure, adult respiratory distress syndrome, disseminated intra-

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vascular coagulopathy, and renal failure. Early recognition and prompt appropriate treatment are expected to reduce the high mortality.[1-3] Dry hot skin suggesting total body fluid depletion coupled with hypotension in heat stroke left many physicians, short of any hemodynamic study support, with the prevailing belief that victims of heat stroke were suffering from marked intravascular fluid depletion. Such a belief encouraged doctors, in an attempt to support the cardiovascular system, to infuse rapidly large amounts of intravenous fluids[1,4] (3000 mL or more) in victims of heat stroke on arrival at heat stroke centers. Such a supportive measure has been associated with 35% to 65% incidence of bronchospasm and respiratory distress,[4] which is attributed to aspiration and/or to adult respiratory distress syndrome without adequate hemodynamic assessment to determine cases of pulmonary edema secondary to fluid overload.

A prospective study was designed and conducted in heat stroke centers in Makkah and Mina (holy places for muslim pilgrims from all over the world) in summer 1986. The purpose of the study was to investigate the acute hemodynamic parameters in the early phases of heat stroke and during the cooling process to throw some light on the actual intravascular hydration state and to estimate the average safe intravenous fluid requirement needed to obtain adequate cardiovascular support.

Patients and Methods

Patients were studied upon arrival to the heat stroke center in Mina and Makkah. Inclusion criteria were (1) rectal temperature of 40°C or more; (2) hot dry skin; and (3) central nervous system disturbance (e.g., delirium, semicoma, or coma). All patients fulfilling these criteria and having available the Swan-Ganz insertion team upon arrival to the cooling room were studied regardless of their clinical status. Thirteen patients were studied randomly. Along with cooling initiation, a No. 8 French Cordis subclavian introducer was inserted, and a No. 7 French Swan-Ganz thermodilution catheter was advanced, guided with pressure tracing monitor. Right atrial pressure, right ventricular pressures, pulmonary arterial pressures, and pulmonary capillary wedge pressure (PCWP) were measured. Cardiac output was calculated using thermodilution technique and a thermodilution computer. Pulmonary pressure and PCWP measurements and cardiac output assessment along with systemic blood pressure and heart rate were obtained as frequently as the field management circumstances allowed. Central blood temperature was recorded along with rectal temperature throughout the whole cooling process, and systemic vascular resistance and systemic vascular resistance index, as well as total pulmonary vascular resistance and total pulmonary vascular resistance index were calculated[5] for each recording. Mean time between the diagnosis and hemodynamic study was 15 minutes (range, 10 to 20 minutes). The thermodilution catheter along with the Cordis introducer were removed when the patient's hemodynamic status was thought to be essentially back to normal or when there was a malfunction in the catheter device (one patient). The statistical method used was the Student *t* test. The standard least-squares correlation coefficients were evaluated and tested for significance.

Results

Group 1 comprised eight patients who recovered completely with no pulmonary edema or complications. Their average age was 58.3 ±SD 4.3 years. Group 2 comprised five patients (38%) who had acute respiratory distress with bronchospasm with no evidence of aspiration. Their average age was 63.8 ± SD 8.5 years. (There was no statistical difference in age between the two groups.) All five patients had pulmonary edema, as evidenced both clinically and radiologically, which was confirmed by pulmonary capillary wedge pressure measurement, but they did not qualify for being actual cases of adult respiratory distress syndrome. Two patients in the pulmonary edema group were treated with intravenous sodium nitroprusside drip, and the other three patients were treated with intravenous furosemide (Lasix). One patient from group 2 who was treated with intravenous furosemide never woke from his coma, and he developed disseminated intravascular coagulopathy and renal failure and died after transfer to a referral hospital in Jeddah.

It was estimated that eight patients without pulmonary edema received 400 to 1200 mL of normal saline in the first 4 hours of management, while the five patients in the pulmonary edema group received 1200 to 1800 mL of normal saline in the first 4 hours of management, most within the first hour. The amount of fluid given to an individual patient depended on the physician. Sometimes the patients arrived in the heat stroke center with an intravenous line already in place.

Average rectal temperature on arrival was similar in both groups, 42.56°C ± SD 0.78°C in group 1 versus 41.96 ± SD 0.73°C in group 2, showing no statistical difference.

There was a direct correlation between the cardiac index and the rectal temperature. In group 1, the *r* value was .59 ($P < 0.01$), and in group 2, the *r* value was .89 ($P < 0.001$). The cardiac index was only slightly higher for the rectal temperature in group 2 (Figure 1). The systemic vascular resistance index correlated inversely with rectal temperature. In group 1, the *r* value was .67 ($P < 0.005$), and in group 2, the *r* value was .44 ($P < 0.02$) (Figure 2). The systemic vascular resistance index rose during and after cooling; the rise was completed in 2 to 4 hours in most patients in group 1 and 3 to 6 hours in group 2 (Figure 3).

The average cardiac index was 4.76 ± SD 0.6 L/min/m^2 in group 1. This was slightly higher in group 2, 5.29 ± SD 5.6 L/min/m^2. The high cardiac index went down in 2 to 3 hours in group 1, and this decrease took slightly longer (3 to 4 hours) in group 2 (Figure 4). The average PCWP on inserting the Swan-Ganz catheter in group 1 was 9.0 ± SD 1.4 mm Hg, while in group 2, it was 12.2 ± SD 6.0 mm Hg (no statistically significant difference). The PCWP did not change significantly in group 1 throughout management while it increased sharply in group 2 early after cooling was started. The nitroprusside appeared to act more promptly in decreasing the PCWP than furosemide (Figure 5).

The total pulmonary vascular resistance index did not change significantly during and after cooling in group 1, while it went to high levels in group 2 and responded well to treatment (Figure 6).

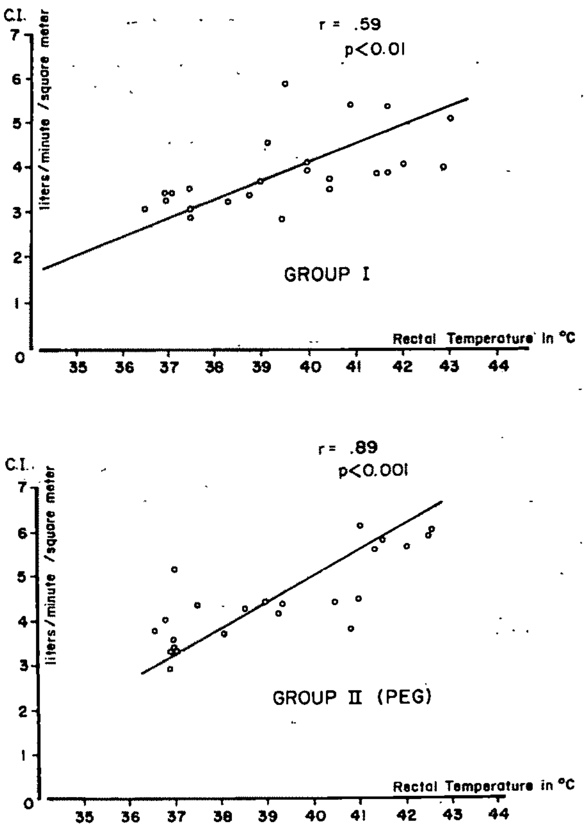

FIGURE 2. Systemic vascular resistance index (SVRI) correlation with rectal temperature.

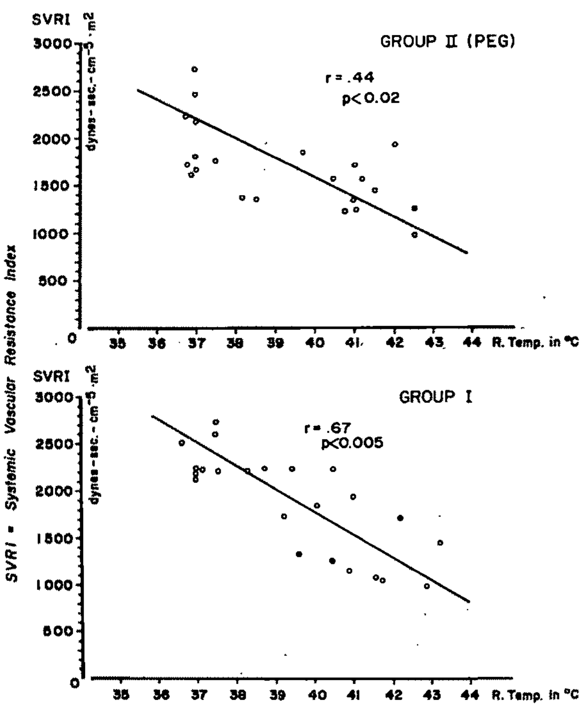

FIGURE 1. Correlation between cardiac index (C.I.) and rectal temperature.

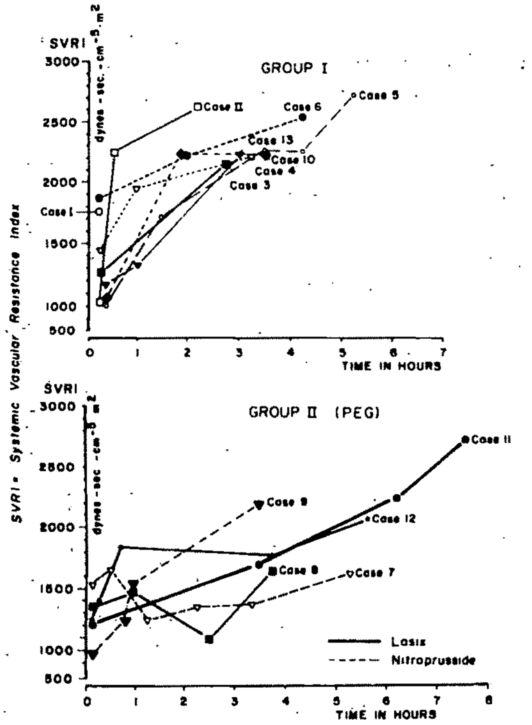

FIGURE 3. Systemic vascular resistance index (SVRI) and its correlation to time.

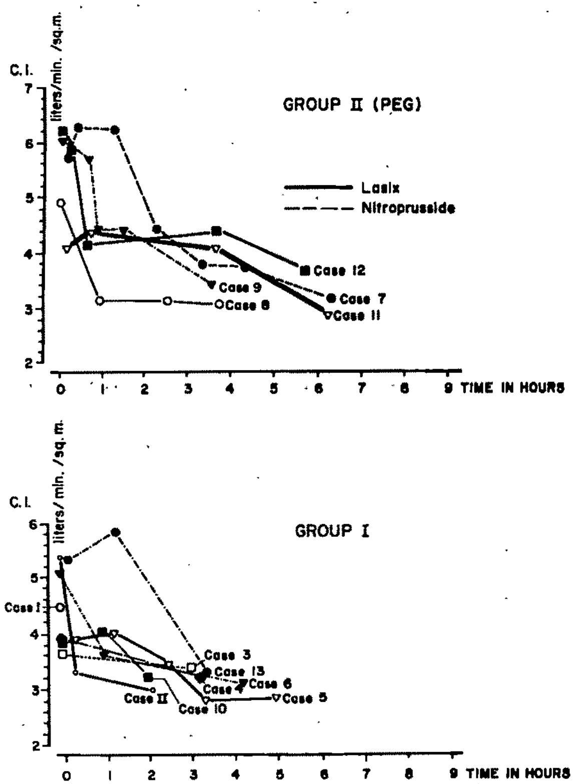

FIGURE 4. Correlation of vascular cardiac index (C.I.) to time.

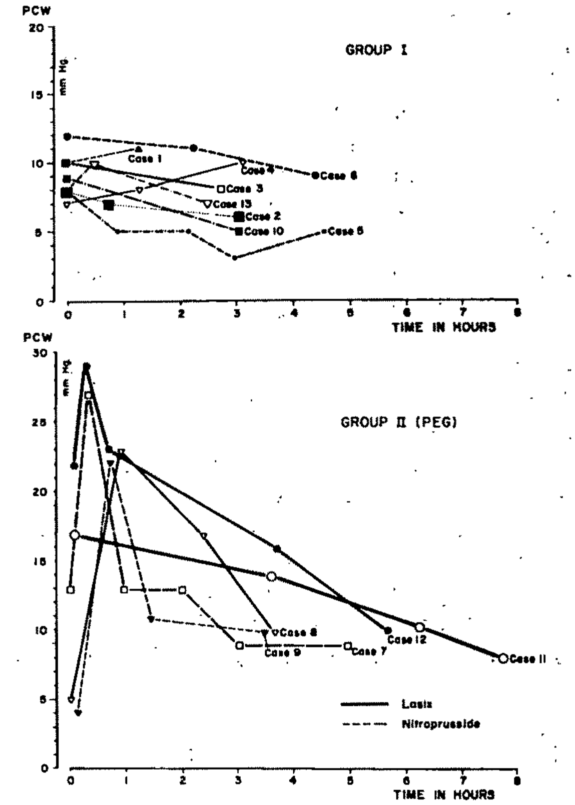

FIGURE 5. Pulmonary capillary wedge (PCW) pressure and its correlation to time.

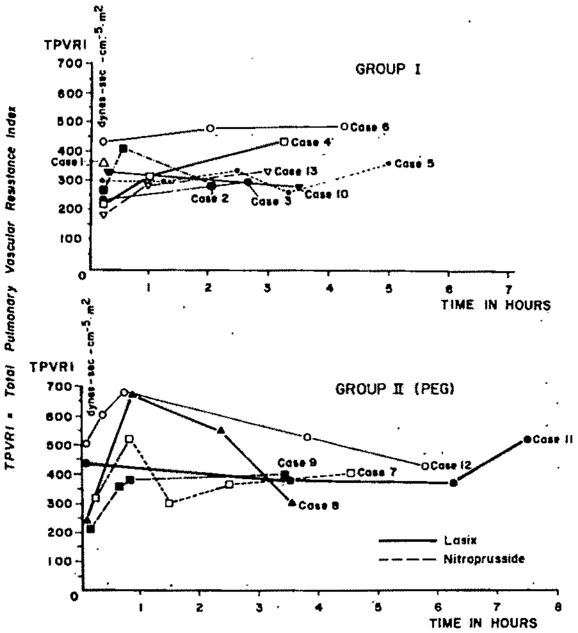

FIGURE 6. Total pulmonary vascular resistance index and its correlation to time.

Discussion

Our data illustrate the fact that high cardiac output in heat stroke is a direct response to the increase in tissue oxygen demand reflected by high rectal temperature. All of our patients showed a high cardiac output response and hyperdynamic circulation and not low cardiac output, as has been reported rarely.[6] The systemic vascular resistance appears to correlate inversely with the rectal temperature in group 1, the patients without pulmonary edema; such a correlation was expectedly attenuated in group 2, the patients with pulmonary edema, due to fluid overload and the pharmacologic therapeutic interventions altering the systemic vascular resistance natural response.

These data lead us to believe that the decrease of systemic vascular resistance in heat stroke causes the hypotension observed in most patients when first seen rather than hypotension being due to intravascular dehydration which appears to be mild. This is evidenced by the fairly good PCWP values on arrival even in patients without pulmonary edema, the group which was not overloaded with fluid early on. Infusing intravenous fluids aggressively seems only to increase the cardiac index a little at the expense of raising the PCWP significantly, producing a state of pulmonary edema. The slightly higher PCWP values on arrival in the pulmonary edema group, which did not reach statistical significance, are probably related to the early and more vigorous intravenous hydration that they received prior to completing the insertion procedure of the Swan-Ganz catheter. The continuation of such an aggressive hydration resulted in a significant rise of PCWP. This rise was early, coinciding with an early but a more gradual rise in systemic vascular resistance. Early increase in vascular tone during cooling translates on the venous side as a limitation in venous capacitance. Such a limitation does not allow the accommodation of rapidly infused intravenous fluids at a time when cooling is also redistributing the blood from the skin-dilated circulatory bed to the central circulation, making it more likely to express the state of fluid overload as acute pulmonary edema.

The cardiac index in group 2 was slightly higher, making it unlikely that the pulmonary edema was due to myocardial failure. The response to sodium nitroprusside drip was prompt, increasing venous capacitance, allowing time for exchange between the excess intravascular fluid and the depleted intracellular compartment to occur. The afterload reducing effect of nitroprusside did not increase the cardiac index at all, attesting to the absence of heart failure as the heart was already working at full capacity. The thermal challenge to the myocardium was similar in the two groups and cannot explain any difference.

We do understand the limitation of our study which involves a small number of patients. Still the study underscores the potential risks of rapid intravenous fluid administration during treatment of heat stroke victims. We cannot rule out completely the existence of myocardial depression in heat stroke, but our unpublished data of systolic function in heat stroke patients by two-dimensional echocardiography in 20 patients suggest that a significant left ventricular dysfunction does not occur.

The only death occurred in one patient with fluid overload who remained unresponsive. It is not clear to us how many cases of brain edema in heat stroke are precipitated by acute fluid overload rather than by thermal injury to the brain; however, this potential hazard should be kept in mind.

Our study also emphasizes the importance of using Swan-Ganz monitoring when bronchospasm and dyspnea develop in heat stroke to avoid labeling these cases as "adult respiratory distress syndrome" by identifying a state of fluid overload which in our group of patients explained all cases of respiratory distress. Such differentiation is critical for management.

Conclusions

Efficient cooling of patients with heat stroke remains the treatment of choice.[7-11] In light of our results, we believe that although victims of heat stroke may have an appreciable total body fluid deficit, it seems that this is mainly at the expense of the intracellular compartment accounting for signs of dehydration while the intravascular compartment manages to keep an adequate circulating volume and avoids significant depletion. The low blood pressure in heat stroke,[12,13] in our experience, is due to low peripheral vascular resistance rather than to significant intravascular depletion or a low cardiac output.

Rapid intravenous fluid administration while cooling patients with heat stroke to correct their hypotension before determining the effect of cooling on their blood pressure seems to be particularly hazardous, because this probably coincides with vasoconstriction and probably a decrease in venous capacitance along with redistribution of blood from the skin to the central circulation, making it even harder to accommodate excess fluid without resulting in pulmonary edema.

In the routine treatment of heat stroke, we recommend administering not more than 1200 mL of normal saline in the first 4 hours of management. In most instances, 700 to 800 mL may be adequate, with later, more gradual repletion of the intracellular compartment with free water intravenously as 5% dextrose/water or orally when the patient is capable of taking fluids by mouth.

The clinician has to individualize treatment in certain cases of obvious continuous volume loss by correcting for it. In cases where there is ambiguity, use of hemodynamic Swan-Ganz monitoring can guide fluid therapy.

Carefully monitored intravenous administration of sodium nitroprusside proved to be safe and effective in treating pulmonary edema in heat stroke. This may particularly help skin perfusion and heat exchange in cases of skin vasoconstriction, and it may also prove particularly helpful in cases of poor tissue perfusion and lactic acidosis.[13,14]

Acknowledgment

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References

1. Shibolet S, Lancaster MC, Danon Y. Heat stroke: a review. Aviat Space Environ Med 1976;47(3):280-301.
2. Jones TS, Liang AP, Kilbourne EM, et al. Morbidity and mortality associated with the July 1980 heat wave in St. Louis and Kansas City, Mo. JAMA 1982;247(24):3327-31.
3. Clowes GH Jr, O'Donnell TF Jr. Heat stroke. N Engl J Med 1974;291:564-7.
4. Soliman SM, Abu Taleb Z, Khogali M, El-Sayed H. Pulmonary aspiration and adult respiratory distress syndrome in 40 cases of heat stroke. In: Heat stroke and temperature regulation. New York: Academic Press, 1983:129-38.
5. Grossman W, ed. Cardiac catheterization and angiography, 3rd ed. Philadelphia: Lea and Febiger, 1986:136-9.
6. O'Donnell TF Jr, Clowes GH Jr. The circulatory abnormalities of heat stroke. N Engl J Med 1972;287:734-7.
7. Stonehill RB, Keil PG. Successful preventive medical measures against heat illness at Lackland Air Force Base. Am J Public Health 1961;51:586-90.
8. Major DA, Finkenstadt E. Heat stroke. In: Oaks WW, ed. Emergency care. New York: Grune and Stratton, 1979:29-39.
9. Weiner JS, Khogali M. A physiological body-cooling unit for treatment of heat stroke. Lancet 1980;1(8167):507-9.
10. Khogali M, Weiner JS. Heat stroke: report on 18 cases. Lancet 1980;2(8189):276-8.
11. Al-Harthi S, Yaqub B, Al-Nozha M, et al. Management of heat stroke patients by rapid cooling comparing a conventional method with a body cooling unit. Saudi Med J 1986;7:369-76.
12. Rowell LB, Brengelmann GL, Murray JA. Cardiovascular responses to sustained high skin temperature in resting man. J Appl Physiol 1969;27:673-80.
13. Costrini AM, Pitt HA, Gustafson AB, Uddin DE. Cardiovascular and metabolic manifestations of heat stroke and severe heat exhaustion. Am J Med 1979;66(2):296-302.
14. Stadnyk AN, Glezos JD. Drug-induced heat stroke. Can Med Assoc J 1983;128(8):957-9.

A RETROSPECTIVE STUDY OF THE IMPACT OF AN EXPANDED PROGRAM OF IMMUNIZATION ON TARGET DIESEASES IN SAUDI ARABIA

Ahmed S. Hafez, MD, PH

أجريت دراسة استعادية لتحديد أثر البرنامج الموسع للتمنيع خلال السنة الأولى من العمر واتجاهات تحول الأمراض المقصودة في الأعوام ١٩٨٣ - ١٩٨٦م في المملكة العربية السعودية. كان جمهور الدراسة المقصود هو مجموع المواليد المسجلين في كل من هذه السنوات. تم جمع حالات الأمراض المقصودة وعدد المواليد المنعين وفقا للجنس وجرعة اللقاح باستخدام نموذج تم اعداده مقدما من التقارير الصحية السنوية في المملكة العربية السعودية. تم تقدير نسبة تغطية التلقيح وفقا للجنس، وجرعة اللقاح وكذلك النسبة المرجحة لتغطية التلقيح في السنة الأولى من العمر لكل سنة. كما تم احتساب المعدل التراكمي المتوسط للاصابة بالأمراض المقصودة خلال الفترة نفسها. أشارت مقارنة هذه النتائج مع تلك التي تمت في عام ١٩٨٣م إلى وجود زيادة في معدل التلقيحات ضد الدرن، الخناق، السعال الديكي، الكزاز، شلل الأطفال، والحصبة خلال عامي ١٩٨٤م و١٩٨٦م، ولكن ليس خلال عام ١٩٨٥م، وانخفضت معدلات الاصابة بالأمراض المقصودة خلال عامي ١٩٨٤م و١٩٨٦م.

A retrospective study was undertaken to determine the impact of an expanded program of immunization in the first year of life and trends of the target diseases in Saudi Arabia during 1983-1986. Registered births were the target population each year. Cases of target diseases and the number of vaccinated infants by type and dose of vaccine were collected on a predesigned form from the Annual Health Reports of Saudi Arabia. The vaccination coverage percent by type, dose of vaccine, and the weighted average vaccination coverage percent in the first year of life were estimated per year. The proportional morbidity rate of cumulative target diseases during the same period was also calculated. Results compared to 1983 showed increased vaccination against tuberculosis, diphtheria, pertussis, tetanus, poliomyelitis, and measles during 1984 and 1986 but not in 1985, and morbidity from the target diseases declined during 1984 and 1986.

Health services and socioeconomic factors affecting quality of life are closely related. Primary health care differs from country to country and from urban to rural areas within the same country depending on the availability of resources.[1] In Saudi Arabia, essential health services have been designed to integrate preventive, curative, and rehabilitative approaches. The disease surveillance system in general and the expanded program of immunization for specific target diseases in particular have been strengthened during the past 3 years in Saudi Arabia (based on unpublished data on neonatal survey in Asir and Gizan regions during 5-29 December 1987). Central coordination of surveillance activities and disease reporting in Saudi Arabia is the responsibility of the Directorate of Communicable Diseases Control and Statistics Section of the Ministry of Health.[2]

Immunization programs in developing countries reduce morbidity and mortality from target

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diseases.[3] Immunization against these diseases during the first year of life raises the immunity of the population, and consequently the morbidity from target diseases is decreased. Many national programs shift the primary concern of expanded immunization to disease control.[4] Many countries have reduced measles, pertussis, and poliomyelitis morbidity and mortality to low levels, although measles elimination remains beyond the reach of most countries.[4] Moreover, vaccination against neonatal tetanus is lowest in the developing world, resulting in higher morbidity and mortality.[5] The elimination of neonatal tetanus should be an essential goal of primary health care which can be achieved easily by increasing the immunization coverage in women of child-bearing age, especially pregnant women, with tetanus toxoid and improved maternal prenatal care.[6]

Recently, it has been reported that cases of pertussis and poliomyelitis had significantly decreased whereas diphtheria and measles increased in Saudi Arabia.[2] The literature shows a paucity of studies focusing on the impact of immunization programs on the target diseases in Saudi Arabia. Therefore, the present study was conducted to show the effects of expanded immunization programs on target diseases in Saudi Arabia during 1983-1986. The study was based on the hypothesis that immunization during the first year of life raises the communal immunity of the population.

Methods

This retrospective study was carried out by collecting and compiling the information on predesigned forms from the Annual Health Reports of Saudi Arabia.[7-9] The study population comprised registered births per year. Cases of target diseases in patients of all ages as well as the number of vaccinated infants by type and dose of vaccine were collected from the Annual Health Reports of Saudi Arabia for each year during 1983-1986.[7-9]

The percentage of children vaccinated during the first year of life by type and dose of vaccine was estimated for the study population per year during 1983-1986. The weighted average vaccination rate against target diseases in the first year of life and the proportional morbidity rate of cumulative target diseases to the total reported communicable diseases during the same period were calculated according to methods described by Hill.[10] Statistical analysis of the results was done using suitable tests of significance.[11]

Results

A significant decrease was observed in vaccination coverage during the first year of life in 1985 in subjects receiving tuberculosis (BCG), diphtheria-pertussis-tetanus (DPT), poliomyelitis (OPV), and measles vaccines compared to 1983. The average vaccination percent against overall target disease increased during 1984 and 1986 with a statistically significant decrease during 1985 compared to 1983 (Table 1).

The proportional morbidity of target diseases declined during 1984 and 1985 compared to 1983 with statistically significant differences ($P < 0.001$) except in 1986 (Table 2 and Figure 1). Also, the cases of diphtheria, poliomyelitis, and tetanus (Figure 2) showed a continuous decline during

TABLE 1. *Number and percentage of infants immunized against target diseases by type and dose of vaccine in Saudi Arabia, 1983-1986.*

		Type of vaccine				Weighted average vaccination
Year	Target population	BCG No. (%)	OPV3* No. (%)	DPT3* No. (%)	Measles No. (%)	(%)
1983	239,107	209,561(87.6)	191,707(80.2)	195,219(81.6)	177,839(74.4)	(81.2)
1984	258,100	219,952(85.2)	217,645(84.3)	218,002(84.5)	205,865(79.8)	(83.5)
1985	274,546	204,090(74.3)†	211,481(77.0)†	219,060(79.8)†	201,371(73.3)†	(76.2)†
1986	290,854	225,686(77.6)	259,003(89.0)	257,168(88.4)	228,125(78.4)	(83.7)

*Number 3 indicates third dose received.

†Test of significance (Z) was done to compare 1983 with each of the subsequent years; $P < 0.001$.

TABLE 2. *Proportional morbidity rate of target diseases in Saudi Arabia, 1983-1986.*

	Year			
	1983	1984	1985	1986
Diseases	No. (%)	No. (%)	No. (%)	No. (%)
Immunization target disease	53,861(20.9)	36,263(18.4)	23,066(18.0)*	26,649(26.3)*
Other specified communicable disease	203,900(79.1)	160,453(81.6)	104,866(82.0)	74,642(73.7)
Total	257,761(100.0)	196,716(100.0)	127,932(100.0)	101,291(100.0)

*Test of significance (χ^2) was done to compare 1983 with each of the subsequent years; $P < 0.001$.

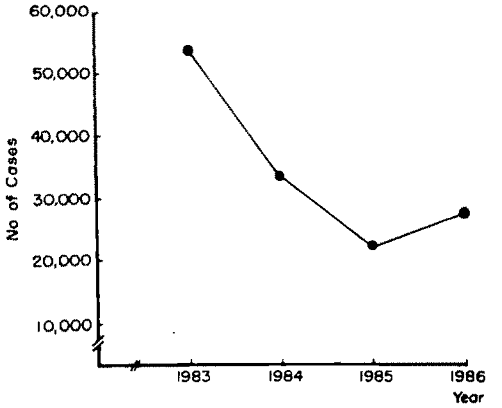

FIGURE 1. Overall pattern of target diseases in Saudi Arabia during 1983-1986.

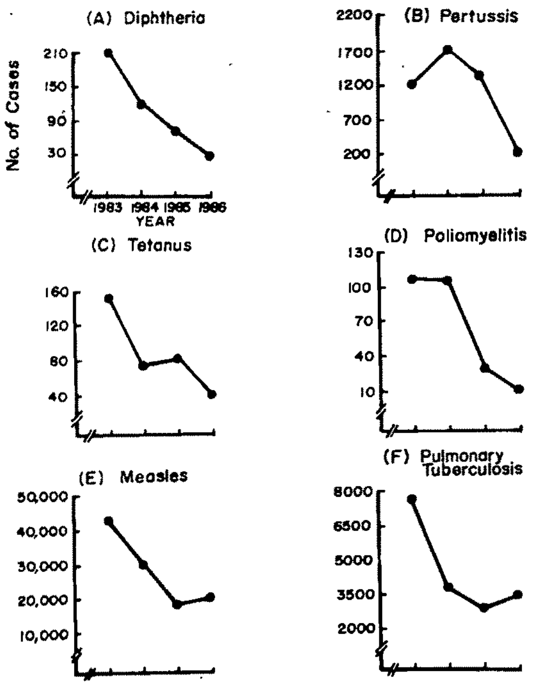

FIGURE 2. Pattern of specific target diseases in Saudi Arabia during 1983-1986.

1984-1986 compared to 1983. Cases of measles and pulmonary tuberculosis decreased in 1984 and 1985 followed by a gradual increase in 1986. Pertussis showed a slight increase during 1984 followed by a continuous decline in 1985 and 1986 compared to 1983 (Figure 2B). Analysis of the various target diseases revealed that the number of cases of diphtheria, pertussis, poliomyelitis, tetanus, measles, and pulmonary tuberculosis had decreased in 1986 by 84.3%, 79.5%, 65.8%, 88.8%, 48.9%, and 51.1%, respectively, in comparison to 1983.

Discussion

In Saudi Arabia, there is a general impression that vaccination against childhood diseases has not been satisfactory.[3] However, the results of this study showed increased use of BCG, OPV, DPT, and measles vaccines during the first year of life during the study period 1983-1986, except in 1985 (Table 1). This agrees with the study carried out during 1985 in Saudi Arabia among clusters of children studied for target diseases.[2] A significant improvement was observed in vaccination against target diseases during 1983-1986 in the Asir Province[12] and during 1984 in the Hail region in Saudi Arabia.[2]

Increased measles vaccination may be explained by the 1983 Royal Decree making measles vaccination compulsory for receiving the birth certificate. The significant decrease in vaccination during the first year of life in 1985 compared to 1983 and 1984 may be attributed to decreased financial budget for health services in 1985 compared to 1983 and 1984.[9]

The continuous decline in the proportional morbidity from target diseases observed during

1984 and 1985 compared to 1983 (Table 2 and Figure 1) may be due to the improved vaccination coverage against target diseases during 1983 and 1984 (Table 1), assuming that all other factors remained constant. The increased proportional morbidity and cumulative target diseases in 1986 were due to an increased number of cases of measles and pulmonary tuberculosis (Figure 2). This increase may represent either an actual increase in these diseases or may be due to a better reporting system.

The decreased number of cases of diphtheria, pertussis, poliomyelitis, tetanus, measles, and pulmonary tuberculosis shown in Figure 2 agreed with that reported in Asir Province[12-14] and data from the Saudi Ministry of Health Surveillance.[2] The World Health Organization in 1987 reported that epidemiologically poliomyelitis has continued to abate worldwide due to the high level of immunization.[15] Further, data from Gambia suggest that vaccination of 70% of the population with three doses of OPV may be effective in elimination of clinical poliomyelitis.[15] Elimination of measles can be achieved by vaccination of 93.5% to 96% of the population against the disease.[16]

Based on this study, it can be concluded that with increased vaccination against target diseases in Saudi Arabia, the number of cases of target diseases decreased. Accordingly, intensive surveillance activities in the reporting system with more immunization coverage against target diseases in general and against measles in particular are recommended in Saudi Arabia. Also, a long-term prospective study at the national level may be of immense help to focus attention on the incidence of target diseases. Such a study will provide nationwide baseline data to assist health planners, especially those concerned with disease prevention.

References

1. World Health Organization. Primary health care. Report of the International Conference on Primary Health Care, Alma Ata, USSR, 6-12 September 1978. Geneva: WHO, UNICEF, 1978;37-71.
2. Report of the Joint Kingdom of Saudi Arabia/WHO/UNICEF Review Mission. Primary health care and immunization programmes in Saudi Arabia, 16 February-13 March 1985. WHO-EM/PHC/31, WHO-EM/IM2/39, April 1985.
3. Strassburg MA. Guidelines for the investigation and control of out-breaks of EPI target diseases. World Health Organization, EPI-Gen/84/Rev 1, 1984:1-59.
4. World Health Organization. Expanded programme on immunization: global advisory group. Wkly Epidemiol Rec 1987;62(3):5-12.
5. World Health Organization. Expanded programme on immunization: global status report. Wkly Epidemiol Rec 1987;62(33):241-8.
6. Stanfield JP, Galazka A. Neonatal tetanus in the world today. Bull WHO 1984;62(4):647-69.
7. Annual Health Report, Ministry of Health, Kingdom of Saudi Arabia, 1403AH:179-238.
8. Annual Health Report, Ministry of Health, Kingdom of Saudi Arabia, 1405AH:171-240.
9. Annual Health Report, Ministry of Health, Kingdom of Saudi Arabia, 1406AH:5-225.
10. Hill AB. The average and further fallacies and difficulties. In: Selwyn T, ed. A short textbook of medical statistics. London: Hodder and Stoughton, 1980;71-2, 266-72.
11. Bourke GJ, Daly LE, McGilvray J. Hypothesis testing: comparison of two or more groups; statistical tables. In: Interpretation and uses of medical statistics. 3rd ed. London: Blackwell Scientific Publications, 1985:112-5,269-71.
12. Hafez AS. A vaccination programme and its impact on the pattern of expanded programme on immunization target diseases in Asir Province, Saudi Arabia. Saudi Med J 1989;10(1):58-61.
13. World Health Organization. Expanded programme on immunization: programme review. Wkly Epidemiol Rec 1986;61(43):329-36.
14. Al-Qahatani MY. A case study of rural health services in Abha. Master's thesis, College of Administrative Sciences, King Saud University, Riyadh, 1985:16-7.
15. World Health Organization. Expanded programme on immunization: control of poliomyelitis. Wkly Epidemiol Rec 1985;60(10):69-76.
16. World Health Organization. Expanded programme on immunization: immunization coverage. Wkly Epidemiol Rec 1987;62(10):61-8.

SYNDROMAL AND NONSYNDROMAL CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN KUWAIT

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اجريت هذه الدراسة في المركز الطبي الكويتي للوراثيات بين عامي ١٩٨٤و ١٩٨٦م، وشملت ١٦٦ من المرضى المصابين بالشفة المشقوقة مع الاصابة بالحنك المشقوق أو بدونها. وبلغ معدل الوقوع في كل من عامي ١٩٨٥م و ١٩٨٦م ١ر٥١ / ١٠٠٠ و ١ر٥٦ / ١٠٠٠ من المواليد الأحياء على التوالي. كانت نسبة الذكور إلى الاناث ١ : ١ر١٥. وتبين وجود قربى الأبوين في ٤٤ر٦٪ من الحالات. كما كانت معظم الحالات (٩٠ر٤٪) فردية، و ٩ر٦٪ منها عائلية. وبلغت نسبة المصابين بالشفة المشقوقة فقط ٤٠ر٤٪، وبالحنك المشقوق ٩ر٦٪، واشتركت الحالتان في ٥٠ر٠٪. كذلك بلغت النسبة المسجلة لحالات انشقاق الشفة المنفرد (غير التلازمي) ٤٤ر٠٪، في حين بلغت نسبة الحالات المصحوبة بمتلازمات معروفة ٣٦ر١٪، وكانت هناك نسبة ١٩ر٩٪ من الحالات دون تشخيص. كما تبين وجود زيغ صبغي في ٩ر٠٪ من الحالات، وسببيات عائدة إلى صفات جسمية مقهورة في ٥ر٤٪، وإلى صفات جسمية قاهرة في ٦ر٠٪، وإلى عوامل متعددة ٤١ر١٪، وإلى عوامل بيئية ١ر٨٪، وإلى عوامل وراثية غير مؤكدة، أو غير محددة، في ٣٦ر٧٪ من هذه الحالات.

This study involved 166 patients with cleft lip with or without cleft palate ascertained at the Kuwait Medical Genetics Centre between 1984 and 1986. The 1985 and 1986 incidence rates were 1.51/1000 and 1.56/1000 livebirths, respectively. The male/female ratio was 1:1.15. Consanguinity was found in 44.6%. Most of the cases (90.4%) were sporadic, while 9.6% were familial. Single cleft lip was detected in 40.4%, cleft palate in 9.6%, and combined cleft lip and cleft palate in 50.0%. Isolated clefting was recorded in 44.0%, while clefting associated with known syndromes was recorded in 36.1%, and 19.9% were undiagnosed. A chromosomal aberration was found in 9.0% of patients; autosomal recessive etiology was noted in 5.4%, autosomal dominant 6.0%, multifactorial 41.0%, environmental 1.8%, and genetically uncertain or undetermined in 36.7%.

Cleft lip with or without cleft palate and isolated cleft palate are among the most common congenital malformations.[1-7] Syndromal and nonsyndromal forms exist. The mode of inheritance and the role of environmental factors are not entirely clear.[8] The incidence varies from 1 to 3 per 1000 births.[7,9-11]

Here we describe 166 cases of cleft lip with or without cleft palate or cleft palate alone diagnosed between 1984 and 1986. The etiology, mode of inheritance, incidence, and classification are discussed.

Subjects and Methods

A retrospective study was conducted of all patients with cleft lip with or without cleft palate

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who attended the Kuwait Medical Genetics Centre between 1984 and 1986. These patients were referred from different health centers and hospitals located in Kuwait. Of the 166 patients with cleft lip and/or cleft palate included in this study, 54 were delivered in the Maternity Hospital. Clinical evaluation assessed pedigree and included relevant investigations, such as blood analysis, amino acid chromatography, radiologic study, chromosomal study, and computed tomographic (CT) scan. Newborn cases were followed through their first month of life. For comparative purposes, 166 control newborns were randomly selected from neonates undergoing screening for hypothyroidism and phenylketonuria whose tests were normal. The matching variables for patient and control groups were sex and nationality. The Z-normal test was used to assess the significance between two proportions. The chi-square test was used to evaluate the significance of seasonal variations, and the logistic regression model[12] was used to order the significance of the contributing factors after fixing the effect of other confounding variables.

Results

The present study included 166 patients suffering from cleft lip with or without cleft palate or cleft palate alone. The female-male ratio was 1.16:1; however, the difference was not statistically significant (Table 1). Most of the patients (79.5%) were seen at the age of less than 1 month. Studying the various nongenetic factors that could affect the occurrence of cleft lip and cleft palate revealed that there was no significant effect of parental age, consanguinity, or seasonal variation. On the other hand, the stepwise logistic regression[12] was used to order the significance of the contributing factors after adjusting for the confounding effect of other variables. It was found that two variables–preconception and first-trimester exposure to teratogens–were statistically significant ($P < 0.001$). Consanguinity and maternal and paternal ages were not statistically significant. Distribution of the patients according to the type of clefting (Table 1) revealed that 44.0% suffered from isolated clefting (cleft lip and/or cleft palate) or cleft palate alone, while 56% had associated syndromes, whether delineated (36.1%) or undelineated (19.9%).

In the present study, the incidence of cleft lip and cleft palate or cleft palate alone found in the Maternity Hospital was estimated to be 1.5/1000 livebirths in 2 successive years; these findings are consistent with oriental estimates. The relatively small difference between sexes may be explained on the basis of the inclusion of many syndromes which show no sex predilection. Unilateral cleft lip was more frequent in males (63.6%), isolated cleft palate was more frequent in females (71.0%), and the combined anomaly was more frequent in females (56.7%). In the present study, the involvement of the females (53.6%) was higher than that of males (46.4%), although this difference was not statistically significant.

The distribution of type of clefting according to sex is illustrated in Table 2, while Tables 3 and 4 display the distribution of the patients according to associated syndromes and chromosomal aberrations, respectively.

Discussion

Cleft lip with or without cleft palate and isolated cleft palate are among the more common congenital anomalies. They may occur alone or as part of genetic syndromes associated with multiple malformations of unknown etiology or syndromes resulting from chromosomal aberrations.[7] The incidence of cleft lip and/or cleft palate has been reported to vary from 0.4 to 3.0/1000 births, with the lowest incidence reported among Africans.[7-11,17] Isolated cleft lip may be unilateral (left side 70% and right side 30%) or bilateral.[11] Isolated cleft palate is rarer than cleft lip and/or cleft palate, with an average frequency of about 0.45/1000 births with little racial variation.[18] The differences of frequencies in different geographic regions and populations may raise the suggestion of an environmental role as well as the difference in the face shape.[17]

The frequency of the associated anomalies with cleft lip and cleft palate varies from one study to another. In the literature the frequency of associated anomalies varies from 3% to over 30%.[19-22] In the present study 56.0% of the cases were associated with other anomalies, of which 36.1% were delineated and 19.9% were undelineated. A recent study showed that over half of the children with cleft lip and/or cleft palate at a large metropolitan center had associated

TABLE 1. *The characteristics of the patients.*

Characteristic	No. (%)
Sex	
Male	77(46.4)
Female	89(53.6)
Age	
≤ 1 mo	132(79.5)
< 1 y	25(15.0)
1–5 y	9(5.5)
Month of delivery	
January–March	43(25.9)
April–June	38(22.9)
July–September	26(15.7)
October–December	54(32.5)
Unknown	5(3.0)
Maternal age (y)	
≤ 20	6(3.6)
20–34	121(72.9)
35–39	13(7.8)
40–44	5(3.0)
45+	2(1.2)
Unknown	19(11.4)
Paternal age (y)	
≤35	73(44.0)
35–39	31(18.7)
40–44	18(10.8)
45–49	8(4.8)
50+	7(4.2)
Unknown	29(17.5)
Parental consanguinity	
Consanguineous	74(44.6)
Nonconsanguineous	69(41.6)
Unknown	23(13.8)
Preconception exposure to teratogens	
Exposed	18(10.8)
Nonexposed	130(78.3)
Unknown	18(10.8)
1st trimester exposure ot teratogens	
Exposed	27(16.3)
Nonexposed	120(72.3)
Unknown	19(11.4)
Amniotic fluid	
Oligo	2(1.2)
Average	133(80.1)
Poly	21(12.6)
Unknown	10(6.0)
Term of pregnancy	
Preterm	24(14.5)
Term	141(84.9)
Post-term	1(0.6)
Type of clefting	
Cleft lip	67(40.4)
Cleft palate	16(9.6)
Cleft lip ± cleft palate	83(50.0)
Severity of clefting	
Unilateral cleft lip	11(6.6)
Unilateral cleft palate	85(51.2)
Unilateral cleft lip ± cleft palate	31(18.7)
Bilateral cleft lip ± cleft palate	39(23.5)
Submucus cleft	–
Mode of inheritance	
Chromosomal	15(9.0)
Autosomal recessive	9(5.4)
Autosomal dominant	10(6.0)
Multifactorial	68(41.0)
Environmental	3(1.8)
Genetic uncertain/undetermined	61(36.7)
Associated syndromes	
Isolated	73(44.0)
Associated with known syndrome	60(36.1)
Undiagnosed	33(19.9)

TABLE 2. *Distribution of patients according to sex and type of anomalies.*

	Male	Female	Total
Type of anomaly	No. (%)	No. (%)	No. (%)
Isolated	34(20.5)	39(23.5)	73(44.0)
Associated with syndrome	26(15.7)	34(20.5)	60(36.1)
Undiagnosed	17(10.2)	16(9.6)	33(19.9)
Total	77(46.4)	89(53.6)	166(100.0)

TABLE 3. *Specified syndromes associated with cleft lip with or without palate.*

Syndrome	No.
Pierre Robin syndrome	16
Kniest's syndrome	4
Meckel-Gruber syndrome	4
Galactosemia	1
Apert's syndrome	1
Orofaciodigital syndrome	1
Amniotic band	1
Spondyloepiphyseal dysplasia	1
VATER association	1
Occipital encephalocele	1
Aase-Smith syndrome	1
Holoprosencephaly	4
Beckwith-Wiedemann syndrome	1
Ectrodactyly-ectodermal dysplasia-clefting syndrome	3
Epignathia	1
Phocomelia	2
Van der Woude's syndrome	1
Popliteal pterygium syndrome	1
Treacher Collins syndrome	1
Cornelia de Lange's syndrome	1
Spondylothoracic dysplasia	1
Total	48

TABLE 4. *Identified chromosomal aberrations associated with cleft lip and cleft palate.*

Chromosomal aberrations*	No.
Trisomy 13	9
Trisomy 18	3
46,XX,t(2;10)(q31;q26)pat†	1
46,XY,del(7)(pter-q32)	1
46,XX,5p-	1
46,XX,del(2)q33	1
46,XX(15p+)	1
46,XY,18p+	1
Total	18

*Eight males and 10 females.
†Paternal origin.

anomalies.[23] Another study including 1000 patients with clefting showed a higher incidence of 63.4%. Half of these children had multiple anomalies corresponding to delineated syndromes, sequences, or association.[23] Today, it is known that clefting occurs in over 250 syndromes.[23]

The genetics of cleft lip and/or cleft palate and isolated cleft palate have been studied by many investigators in various regions and countries. The mode of inheritance and role of environmental factors have not been entirely explained. It is generally accepted that cleft lip and/or cleft palate and isolated cleft palate are developmentally and genetically different. Isolated cases may be explained, according to most authors, by multifactorial inheritance.[2,3,8,16,24,25] However, multifactorial models were not completely fulfilled,[26] thus suggesting heterogeneity of the disorder. Isolated nonsyndromic cleft palate is thought to be etiologically heterogeneous.[26-29] Multifactorial threshold explanation for cleft palate is postulated in most cases.[28,30,31] Mendelian pedigrees for cleft palate have been well documented.[32-34] Usage of complex segregation analysis under a mixed model could not discriminate between single locus and polygenic inheritance. Recent discussion of the origin of sporadic cases[35] showed that the classification of cleft into sporadic and familial groups may be useful in certain analytical contexts. This classification is potentially erroneous although the exact number in error is impossible to define at present. What appears to be a sporadic case at birth may be the only liveborn cleft remaining of several cleft cases conceived, since prenatal selection eliminates a substantial fraction of malformed conceptuses through embryonic and fetal mortality. Thus, the number of truly sporadic cases is smaller than the number of sporadic cases observed at birth.

In the present study, the association of cleft lip and cleft palate or isolated cleft palate with other anomalies constituting undelineated syndromes was found in 19.9%. These anomalies were not constant and involved different body organs in different patients. These cases need further investigation and follow-up to define the underlying syndrome. Due to the relatively high frequency of associated anomalies observed in this study, thorough examination of any patient with cleft lip and/or cleft palate is suggested with careful follow-up until a definite diagnosis is made.

References

1. Curtis E, Fraser FC, Warburton D. Congenital cleft lip and palate, risk figures for counselling. Am J Dis Child 1961;102:853-7.
2. Woolf CM. Congenital cleft lip: a genetic study of 496 propositi. J Med Genet 1971;8:65-83.
3. Carter CO. The inheritance of common congenital malformations. In: Steinberg AG, Bearn AG, eds. Progress in medical genetics. New York: Grune and Stratton, 1965;4:59-74.
4. Chung CS, Ching GH, Morton NE. A genetic study of cleft lip and palate in Hawaii: II. Complex segregation analysis and genetic risks. Am J Hum Genet 1974;26:177-88.
5. Bear JC. A genetic study of facial clefting in Northern England. Clin Genet 1976;9(3):277-84.
6. Welch J, Hunter AG. An epidemiological study of facial clefting in Manitoba. J Med Genet 1980;17(2):127-32.
7. Shiota K. Maternal reproductive loss and cleft lip with or without cleft palate in human embryos. Am J Med Genet 1984;19:121-9.
8. Bonaiti C, Briard ML, Feingold J, et al. An epidemiological and genetic study of facial clefting in France: I. Epidemiology and frequency in relatives. J Med Genet 1982;19(1):8-15.
9. Neel JV. A study of major congenital defects in Japanese infants. Am J Hum Genet 1958;10:398-445.
10. Morton NE. Birth defects in racial crosses. In: Fraser FC, McKusick VA, eds. Congenital malformations. Proceedings of the Third International Conference. Amsterdam: Excerpta Medica, 1970:264-74.
11. Goodman RM, Gorlin RJ. Facial clefts, usual and unusual. In: The malformed infant and child: an illustrated guide. New York: Oxford University Press, 1983:56-7.
12. Engelman L. In: Dixon WJ, ed. Stepwise logistic regression in BMDP statistical soft ware. Berkeley: University of California Press, 1985:330-46.
13. Lowry RB, Trimble BK. Incidence rate for cleft lip and palate in British Columbia 1952-71 for North American Indian, Japanese, Chinese and total populations: secular trends over twenty years. Teratology 1977;16(3):277-83.

14. Cohen MM Jr. Syndromes with cleft lip and cleft palate. Cleft Palate J 1978;15(4):306-28.
15. Melnick M, Bixler D, Fogh-Anderson P, Conneally PM. Cleft lip +/− cleft palate: an overview of the literature and an analysis of Danish cases born between 1941 and 1968. Am J Med Genet 1980;6(1):83-97.
16. Fujino H, Tashiro H, Sanui Y, Tanaka K. Empirical genetic risk among offspring of cleft lip and cleft palate patients. Jpn J Hum Genet 1967;12:62-8.
17. Fraser F, Pashayan H. Relation of face shape to susceptibility to congenital cleft lip: a preliminary report. J Med Genet 1970;7:112-7.
18. Nora JJ, Fraser FC. Cleft lip and cleft palate. In: Medical genetics: principles and practice, 2nd ed. Philadelphia: Lea and Febiger, 1981:307-11.
19. Fraser FC. The genetics of cleft lip and cleft palate. Am J Hum Genet 1970;22:336-52.
20. Pashayan HM. What else to look for in a child born with cleft of the lip and/or palate. Cleft Palate J 1983;20(1):54-82.
21. Knox G, Braithwaite F. Cleft lips and palates in Northumberland and Durham. Arch Dis Child 1963;38:66-70.
22. Greene JC, Vermillion JR, Hay S, et al. Epidemiologic study of cleft lip and cleft palate in four states. J Am Dent Assoc 1964;68:386-404.
23. Shprintzen RJ, Siegel-Sadewitz VL, Amato J, Goldberg RB. Anomalies associated with cleft lip, cleft palate, or both. Am J Med Genet 1985;20(4):585-95.
24. Czeizel A, Tusnadi G. An epidemiologic study of cleft lip with or without cleft palate and posterior cleft palate in Hungary. Hum Hered 1971;21:17-38.
25. Melnick M, Shields ED, Bixler D. Studies of cleft lip and cleft palate in the population of Denmark. In: Melnick M, Bixler D, Shields ED, eds. Etiology of cleft lip and cleft palate: progress in clinical and biological research. New York: Alan R. Liss, 1980:225-48.
26. Shields ED, Bixler D, Fogh-Andersen P. Cleft palate: a genetic and epidemiologic investigation. Clin Genet 1981;20(1):13-24.
27. Carter CO, Evans K, Coffey R, et al. A three generation family study of cleft lip with or without cleft palate. J Med Genet 1982;19(4):246-61.
28. Bixler D. Genetics and clefting. Cleft Palate J 1981;18(1):10-8.
29. Chung CS, Rao DC, Ching GHS. Population and family studies of cleft lip and cleft palate. In: Melnick M, Bixler D, Shields ED, eds. Etiology of cleft lip and cleft palate: progress in clinical and biological research. New York: Alan R. Liss, 1980:325-52.
30. Cohen MM. Craniofacial disorders. In: Emery AEH, Rimoin DL, eds. Principles and practice of medical genetics. New York: Churchill Livingstone, 1983:576-621.
31. Fraser FC. Animal models for craniofacial disorders. In: Melnick M, Shields ED, Bixler D, eds. Etiology of cleft lip and cleft palate: progress in clinical and biological research. New York: Alan R. Liss, 1980:12.
32. Lowry RB. X-linked cleft palate. Birth Defects 1971;7(7):76-86.
33. Rushton AR. Sex-linked inheritance of cleft palate. Hum Genet 1979;48(2):179-81.
34. Jenkins M, Stady C. Dominant inheritance of cleft of the soft palate. Hum Genet 1980;53(3):341-2.
35. Dronamraju KR, Bixler D. Fetal mortality in oral cleft families (V): studies of sporadic vs familial and pure vs syndromic clefts. Clin Genet 1984;25(4):314-7.

Special Communication

A PRACTICAL GUIDE TO THE USE OF A PAVLIK HARNESS FOR THE TREATMENT OF DISLOCATED HIP IN INFANTS

Hugh G. Watts, MD

جهاز بافليك مفيد لمعالجة الخلع الولادي للورك لدى الرضع الذين لاتزيد أعمارهم عن ١٠ شهور. يترك الورك بدون رد عند ارتداء الجهاز ويحدث الرد تلقائيًا خلال شهر بعد ارتدائه. وقد كان تطبيق هذا الجهاز في خبرتنا ناجحا لدى مايزيد عن ٩٠٪ من الأطفال. يعطي هذا الجهاز نسبة عالية من الفعالية مقارنة بالتكلفة ويمكن استخدامه بسهولة في المملكة العربية السعودية.

The Pavlik harness is a useful device for treating infants up to 10 months of age with congenital dislocation of the hip(s). The hip is left dislocated when the harness is applied, and the dislocation reduces spontaneously over the next month of harness wearing. In our hands, the technique has been successful in over 90% of children. It is a highly cost-effective system which can be readily used in Saudi Arabia.

The treatment of a child with a dislocated hip is clearly easiest when the diagnosis has been made at birth. However, for orthopedic surgeons working in Saudi Arabia, this is an uncommon event. More likely, the orthopedist is faced with a child who is a few months to 3 or 4 years old. While children over the age of 1 year will require conventional traction, followed by closed reduction for younger children and open reduction for older children, the Pavlik harness is an ideal tool to use in the treatment of the dislocated hip in infants from birth to 8 months of age and perhaps up to 1 year of age.

Many orthopedic surgeons are still not aware that the Pavlik harness can be used for treating the child whose hip is dislocated and have reserved the use of the Pavlik harness only for children with acetabular dysplasia or for the later phases of treatment once the hip is well located. However, it is an established observation[1-5] that an infant whose hip is dislocated can be placed in a Pavlik harness, and without manipulation of the hip, the joint will reduce spontaneously in the harness. The mechanism of this reduction is not understood, which reinforces the disbelief of orthopedic surgeons who have not experienced this phenomenon. The purpose of this paper is to emphasize this important use of the Pavlik harness, to point out that it is a practical and cost-effective technique that has been acceptable to Saudi Arabian families, and to review the details of this technique of management without which the treatment may fail.

Technique

In the past, the infant with the dislocated hip was treated by a prior period of traction. Once the distal movement of the proximal femur had taken place, the hip was reduced under anesthesia and maintained in abduction in a plaster spica. Hip stability was maintained by hip abduction. With the Pavlik harness, the emphasis is on flexion of the hip rather than abduction.

When a dislocated hip is flexed, the point of rotation is at the lesser trochanter (not the femoral head), and the head of the femur moves distally. In the Pavlik harness, the child is then left to kick in the brace, and somewhere between 2 and 4 weeks, the hip usually spontaneously relocates.

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Once the hip relocates, the brace is maintained for another 2 to 3 months to allow the tissues to accommodate to the new relationship of the femoral head inside the acetabulum.

Application of Pavlik Harness

A harness size should be selected so that the "waist" strap fits not around the waist but the chest. If the strap is too low, the strap may interfere with feeding and also makes diaper changing more difficult. The foot straps should be sufficiently tight that the top of the knees are approximately at the level of the umbilicus giving flexion of 100 to 120 degrees. Effort should be made to achieve flexion, and the posterior straps (which control abduction) do not need to be tight. In fact, posterior straps fixed too tightly may be harmful.

When satisfactory adjustments have been made, it is strongly recommended that the loose ends of the straps be covered with adhesive tape so that parents will not be tempted to remove the harness. The only straps which the parent should be allowed to open are the two Velcro closures on the lateral aspect of the chest strap and the booties. The harness stays on 24 hours a day.

Socks should be worn over the feet inside the brace. Parents need to be instructed in how the posterior strap of the foot piece ("bootie") can be opened to change the socks, but the parents must be urged to keep the hip and knee in flexion while this is being performed.

The child's diapers can readily be changed without removal of the harness. The undershirt, which should be worn under the brace, can also be changed without removing the harness by loosening the side straps of the chest strap. The child is bathed by using a wet washcloth around the straps.

Subsequent Management

Parents should be encouraged to have the child lie face down. In Saudi Arabia, where children are largely left to lie flat on their backs, parents are rather alarmed to have a child lie on its face, and such children who have never lain face down may be irritable when initially placed prone until they get used to this position. While prone lying is probably helpful, it is not mandatory.

Once again, it should be pointed out to the parents that this brace is worn full time for several months.

When the patient's initial visit is over, it is strongly advised that the child be brought back in approximately a week for general review with the parents. This visit has been found to be an extremely important one, since parents frequently do not remember all of the instructions in the confusion in the first visit and will be subject to many "helpful suggestions" by well-meaning relatives once they get home.

Following this second visit, the child is seen again in 3 to 4 weeks at which time an anteroposterior roentgenogram of the hips is taken. Usually the hips are relocated at this point. One potential problem is that of overlooking a persisting dislocation. Because of the flexed position of the thigh, the head of the femur shifts inferiorly. If it is still dislocated posterior to the acetabulum, the orthopedic surgeon may not recognize it. One can suspect such a situation if the head of the femur appears to be too close to the acetabulum. The problem can be confirmed by taking "acetabular view" x-rays in the harness which allows the hips to be viewed at right angles to the anteroposterior views (Figures 1 and 2).

If the hips are relocated, the harness is maintained for 2 more months. It is preferable to see the child at the end of 1 month with repeat x-ray films. At that visit, the circumferential straps around the legs may need to be loosened (because of the growth of the legs), and the leg straps may need to be lengthened (again because of growth). Care must be taken to maintain the flexion.

When the hips have been in place for 2 months, the harness is used as a nighttime device. At this point, the child will have spent several months in flexion and will have bilateral hip flexion contrac-

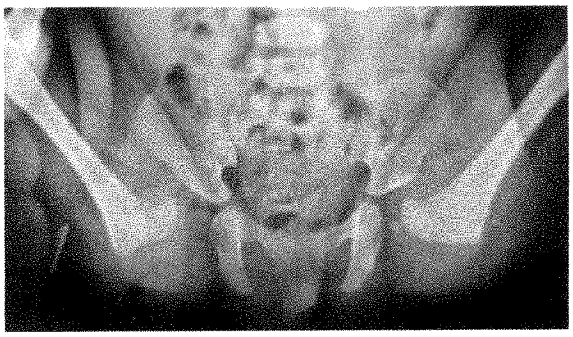

FIGURE 1. Anteroposterior view of 6-month-old girl in a Pavlik harness. Note that the left femur appears to be too close to the acetabulum.

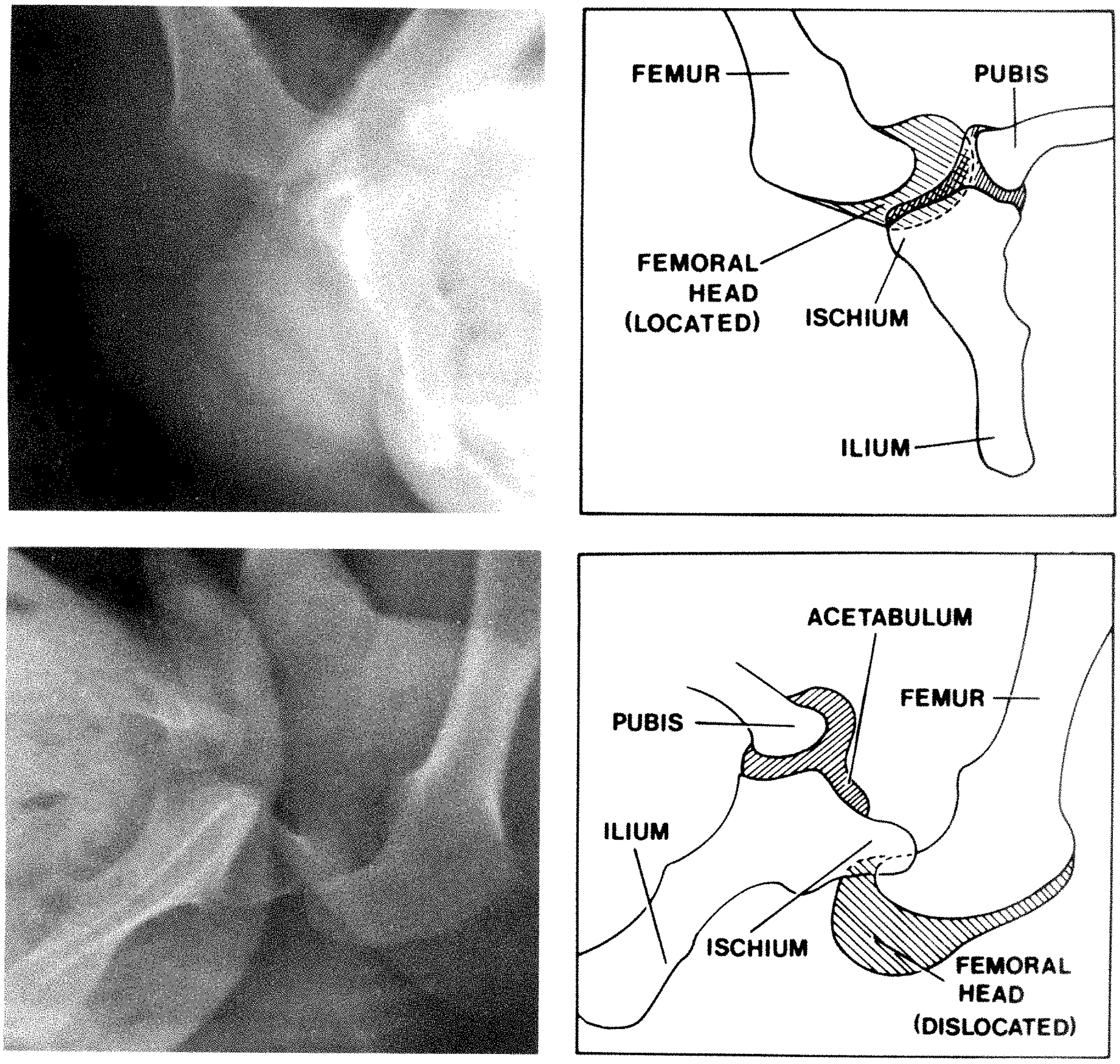

FIGURE 2. Acetabular views of the same child seen in Figure 1. Top, right hip; bottom, left hip. Note that the left hip is posteriorly dislocated.

tures. *This is of no concern*. Some orthopedic surgeons have been alarmed at the flexion contracture and advised parents to do hip extension exercises. This may lead to redislocation of the hips. Children are allowed to do their normal kicking, and these flexion contractures have always resolved spontaneously.

If, at the end of the first month, the hip is *not* relocated, it is important to review the situation and to see if there was something wrong in the wearing of the harness. Primarily the question is "Were the hips flexed enough?" If this has not been the case, it is worthwhile continuing the treatment with adequate flexion. If, however, adequate flexion has been present and the hip is still not relocated, the child should be admitted for more conventional traction and closed reduction. If that should be the case, very little has been lost except 1 month of time during which time the child is at home.

Avascular necrosis has been reported with an incidence of 0.9% to 7.2% with an average of 2.38% in a large multicenter study.[6] The higher incidence of avascular necrosis results from tightening the posterior straps to force hip abduction rather than seeking the goal of hip flexion. When the posterior straps are not done tightly, avascular necrosis has been minimal.

Experience elsewhere has shown that this treatment is effective in approximately 90% of patients. Between July 1984 and March 1987, at the King Faisal Specialist Hospital and Research Centre, 11 Saudi infants (10 girls and 1 boy) ages 1 to 10 months (four over the age of 6 months) were treated by this system. Ten patients relocated their hips spontaneously. There has been no avascular necrosis. The 11th child, a girl, subsequently was admitted to the Hospital for traction, then could not be stably reduced, and ultimately required an open reduction.

Treating children older than 6 months has not usually been recommended in the United States; however, in a large European study, children up to age 11 months had no problems.[6] Children over 1 year of age will not ordinarily tolerate the restriction of a Pavlik harness. There is one report of a child developing valgus of the knees (successfully treated with a brace) after she was treated with a Pavlik harness at 6 months of age[7]; however, this child was treated for an excessive time (8 months).

The cost of a Pavlik harness currently is approximately SR100. (They can also be made locally from webbing straps and buckles.) This is clearly a great deal cheaper than any kind of in-hospital management.

References

1. Ramsey PL, Lasser S, MacEwen GD. Congenital dislocation of the hip: use of the Pavlik harness in the child during the first six months of life. J Bone Joint Surg Am 1976;58-A(7):1000-4.
2. Green WT Jr. Congenital dislocation of the hip treated by the Pavlik harness (abstract). J Bone Joint Surg Am 1976;58-A(2):285.
3. Munger DH. The Pavlik sling in congenital dislocation of the hip (abstract). J Bone Joint Surg Am 1976;58-A(5):736.
4. Iwasaki K. Treatment of congenital dislocation of the hip by the Pavlik harness: mechanism of reduction and usage. J Bone Joint Surg Am 1983;65-A:760-7.
5. Mubarak S, Garfin S, Vance R, et al. Pitfalls in the use of the Pavlik harness for treatment of congenital dysplasia, subluxation, and dislocation of the hip. J Bone Joint Surg Am 1981;63-A:1239-48.
6. Grill F, Bensahel H, Canadell J, et al. The Pavlik harness in the treatment of congenital dislocating hip: report of a multicenter study of the European Paediatric Orthopaedic Society. J Pediatr Orthop 1988;8(1):1-8.
7. Schwentker EP, Zaleski RJ, Skinner SR. Medial knee instability complicating the Pavlik-harness treatment of congenital hip subluxation: case report. J Bone Joint Surg Am 1983;65-A:678-80.

Case Reports

LEIOMYOSARCOMA OF THE INFERIOR VENA CAVA: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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Leiomyosarcoma of vascular origin is a rare and usually lethal tumor. It arises more commonly from large veins than arteries, and more than one half occur in the inferior vena cava.[1] Most of these tumors are diagnosed at autopsy or laparotomy. Surgical resection offers the best prospect of cure; however, the majority of patients die from metastatic lesions into the liver and lungs.

The purpose of this report is to describe two cases of leiomyosarcoma of the inferior vena cava.

Case Reports

Case 1

A 35-year-old Saudi woman was admitted with a 14-year history of an intermittent dull ache in the right hypochondrium. The pain had no relationship to meals, and there was no history of weight loss or other relevant complaints. Physical examination revealed a large, nontender, firm abdominal mass in the right flank. Results of routine hematological investigations, including complete blood cell count, erythrocyte sedimentation rate, urea, and electrolytes, and liver function tests were all normal. Ultrasound examination of the abdomen revealed a 9 × 5 × 9-cm solid mass in the right flank and a single stone in the right kidney. The liver and spleen appeared normal, and there were no other masses in the abdomen or pelvis. Findings on subsequent radiologic investigations, which included chest x-ray, liver and spleen isotope scan, intravenous urogram, and barium enema, were all reported normal.

At laparotomy the mass was retroperitoneal, arising from the inferior vena cava at the level of the right renal vein and extending superiorly to within 2.5 cm of the most inferior hepatic vein. The left renal vein was not involved in the tumor mass. The inferior vena cava was completely occluded. The mass was separated from surrounding structures by sharp and blunt dissection, then completely resected together with the right kidney. The two ends of the inferior vena cava were closed with a continuous suture. There were no other abnormal findings in the abdomen. Postoperative recovery was uneventful. Histopathologic examination of the resected mass showed leiomyosarcoma arising from the inferior vena cava.

The patient is well and alive 23 months later with no signs of metastases or lower limb edema, and renal function is normal.

Case 2

A 55-year-old Saudi woman was admitted for further investigations of right flank pain, which was vague in nature and associated with indigestion and increasing constipation of 7 months' duration. Three months before admission, there was increasing puffiness of the face and swelling of both lower limbs. There was no history of jaundice or shortness of breath, nor was there any history of gynecologic problems. The patient was a known diabetic and had been treated with oral hypoglycemic drugs for the last 9 years. She was moderately obese, and apart from the puffiness of the face and minor edema of the lower limbs, the physical examination was normal.

Laboratory studies showed normal blood cell count, but the ESR was high at 66 mm/h. Blood urea and creatinine were elevated at 12 mmol/L and 185 mmol/L, respectively. The creatinine clearance was 65 mL/min. The liver function tests were normal. Urine examination showed moder-

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ate proteinuria.

Ultrasound examination of the abdomen revealed a hypoechoic mass measuring 6 × 14 × 7 cm, closely related to the inferior vena cava. The liver, spleen, and both kidneys were normal, and there were no other masses in the abdomen or pelvis. The CT scan showed a lobulated mass in the region of the inferior vena cava anterior to the right kidney and extending behind the head of the pancreas upward to the level of the right suprarenal gland.

An isotope renogram was normal. Fine-needle aspiration cytology from the mass under ultrasound control was inconclusive. At laparotomy there were two abnormal findings: (1) 5 × 4-cm rounded firm mass at the mesenteric border of the transverse colon near the hepatic flexure, and (2) a large lobulated retroperitoneal mass arising from and occluding the inferior vena cava at the level just above the right renal vein and extending upward behind the duodenum. Mobilization of the mass from the duodenum and pancreas revealed the superior margin to be just below the entrance of the hepatic veins.

It proved possible to perform a complete surgical clearance by resecting the inferior vena cava from just distal to the hepatic veins above to just proximal to the renal veins below. The two ends of the inferior vena cava were closed with a continuous suture. The two renal veins were thus entering the blind distal stump of the inferior vena cava, but it was clinically apparent that an effective collateral venous circulation had already been well established. The separate mass at the colonic mesenteric border was then excised with a wedge of the transverse colon. The colonic continuity was reestablished by end-to-end anastomosis.

Histopathologic examination of the resected masses showed the inferior vena cava mass to be a leiomyosarcoma and the colonic mass to be a bilharzial granuloma. Postoperative recovery and progress were uneventful, and the patient is alive and well 12 months later. The mild lower limb edema is well controlled by elastic stockings, and renal function remains satisfactory.

Discussion

Perl[2] first described a leiomyosarcoma of the inferior vena cava found at autopsy in 1871. It remains a rare entity, and in a recent review by Bruyninckx and Derksen,[3] only 70 cases could be found in the world literature. Of these, 83% occurred in women, and this female preponderance has led to speculation as to whether the caval lesions are secondary to a primary uterine source.[4] Neither of our two patients had uterine fibromyoma. The tumor can occur at any level in the inferior vena cava, and about one third are sited in the midcaval segment.

Leiomyosarcoma of the inferior vena cava invariably causes diagnostic difficulty, and in only 6% of the reported cases was the lesion suspected preoperatively.[3] The symptomatology is nonspecific, and ill-defined abdominal pain is the most constant complaint. A palpable abdominal mass is present in only one third of the cases. Edema of the legs or other consequences of inferior vena cava obstruction are surprisingly rare, presumably because the slow advancement of the obstructing lesion allows efficient collateral venous development.[1,3,5] Tumors of the upper third of the inferior vena cava are, however, more overt and often present as a variant of the Budd-Chiari syndrome.[5-12] In patients presenting with an abdominal mass, ultrasonography and CT scan should demonstrate the anatomical proximity of the tumor and inferior vena cava. Venacavography will confirm the site of origin and assess the operability. Although our experience with percutaneous fine-needle aspiration cytology was not encouraging, we believe that with increasing experience in this technique, proper preoperative histologic diagnosis will be possible. Sonographic and/or isotope liver scans and chest roentgenography are invaluable in detecting metastatic lesions in the liver and lungs, which are the commonest sites for metastasis. Laboratory investigations are of little help in suggesting the diagnosis except for abnormal values which reveal secondary disorders due to hepatic or renal venous obstruction.[5,13]

Untreated, the lesion is ultimately fatal with widespread metastases.[14,15] Surgical excision offers the only hope of palliation or even cure and is usually feasible in the mid or lower caval segments. Reconstruction of the excised vena caval segment is unnecessary because of the developed collateral circulation. In few reported cases, prosthetic replacement of the inferior vena cava was performed but with very discouraging results.[16,17] In all other reported cases and in our two cases, the continuity of the inferior vena cava was not reestablished, but the procedures were tolerated well and the lower limb edema was infrequent.

We conclude that surgeons should be suspicious of such a tumor involving the inferior vena cava, and surgical excision should be tried as long as the tumor does not involve the upper segment of the inferior vena cava. Adjuvant radiotherapy and/or chemotherapy may be necessary in the presence of metastatic lesions or incomplete resection.

References

1. Kevorkian J, Cento DP. Leiomyosarcoma of large arteries and veins. Surgery 1973;73:390-400.
2. Perl L. Ein fall von sarkom der vena cava inferior. Virchows Arch Pathol Anat 1871;53:378-83.
3. Bruyninckx CM, Derksen OS. Leiomyosarcoma of the inferior vena cava: case report and review of the literature. J Vasc Surg 1986;3(4):652-6.
4. Jonasson O, Pritchard J, Long L. Intraluminal leiomyosarcoma of the inferior vena cava: report of a case. Cancer 1966;19:1311-5.
5. Bailey RV, Stribling J, Weitzner S, et al. Leiomyosarcoma of the inferior cava: report of a case and review of the literature. Ann Surg 1976;18(2):169-73.
6. Harland WA, Clamen M, Rodiguez VM. Leiomyosarcoma of the inferior vena cava with clinical features of Chiari's syndrome. Can Med Assoc J 1960;83:1064-6.
7. Beaird JB Jr, Scofield GF. Budd-Chiari syndrome: hepatic vein occlusion due to leiomyosarcoma primary to the inferior vena cava. Arch Intern Med 1962;110:435-41.
8. Barbier P, Scotto J, Julien C, et al. Leiomyosarcoma dela veine cava inferieure et syndrome de Budd-Chiari. Rev Med Chir Mal Foie 1968;43:1-5.
9. Cardell BS, McGill DA, Williams R. Leiomyosarcoma of inferior vena cava producing Budd-Chiari syndrome. J Pathol 1971;104:283-6.
10. Wray RC Jr, Dawkins H. Primary smooth muscle tumors of the inferior vena cava. Ann Surg 1971;174:1009-18.
11. Justiniani FR, Cohen GH, Roen SA, et al. Budd-Chiari syndrome due to leiomyosarcoma of the inferior vena cava. Am J Dig Dis 1973;18:337-46.
12. Hallock P, Watson CJ, Berman L. Primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease. Arch Intern Med 1940;66:50-4.
13. Gue'don J, Mesnard J, Poison J, et al. Hypertension renovasculaire par leiomyosarcoma de la veine cave inferieure: guerisone de l'hypertension et survie de 2 ans apres intervention chirurgical. Ann Med Interne 1970;121:905-12.
14. Kalsbeek HL. Leiomyosarcoma of the inferior vena cava. Arch Chir Neerl 1974;26:35-40.
15. Patel JK, Englander LS. Leiomyosarcoma of the inferior vena cava. J Surg Oncol 1982;21(4):238-40.
16. Smith DE, Hammon J, Anane-Sefah J, et al. Segmental venous replacement: a comparison of biological and synthetic substitutes. J Thorac Cardiovasc Surg 1975;69(4):589-98.
17. Dale WA, Harris J, Terry RB. Polytetrafluoroethylene reconstruction of the inferior vena cava. Surgery 1984;95(5):625-30.

PAPILLEDEMA AS AN INITIAL MANIFESTATION OF BEHCET'S SYNDROME: REPORT OF FOUR CASES WITH CEREBRAL VENOUS SINUS THROMBOSIS

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Behcet's syndrome as initially described encompassed the triad of oral ulcers, genital ulcerations, and uveitis. Subsequently, erythema nodosum and joint involvement (polyarthritis or arthralgia) were recognized as common associations. Neurologic involvement is common with the incidence varying widely (10%,[1] 20%,[2,3] 49%[4]). Papilledema is said to be a rare manifestation,[4-15] but it may antedate the clinical expression of other systemic signs of Behcet's syndrome.[4,7,8,10,13,14]

Seven patients (six males and one female) with neurologic manifestations of Behcet's syndrome have been seen in our department since August 1983. Four of these patients had papilledema as the presenting manifestation.

Case Reports

Case 1

This 24-year-old Saudi man was referred to King Khalid University Hospital (KKUH) because of bilateral papilledema. He was seen initially in another hospital with a 4-month history of severe headache and blurring of vision. In the presence of a strongly positive Mantoux test, intermittent fever, and cerebrospinal fluid showing 20 lymphocytes, he was placed on antituberculous treatment. Two months later, he developed popliteal vein thrombosis in the right leg as demonstrated by venography.

On examination all systems were normal except for bilateral papilledema and signs of deep vein thrombosis in the right leg. On the ninth day of hospitalization orogenital ulcers typical of Behcet's syndrome developed. There was a temporary remission with relapse 3 weeks later. Results of relevant investigations regarding this patient (and the following three) appear in Table 1. Transvenous digital subtraction angiography (DSA) illustrated almost complete nonvisualization of the sagittal and transverse sinuses indicating thrombotic occlusion (Figure 1). On computed tomographic (CT) scan immediately following DSA, the torcular Herophili was surrounded by contrast medium showing partial recanalization (Figure 2). The patient was treated with prednisolone and anticoagulation for 6 months. Recurrent orogenital ulcers developed during follow-up.

Case 2

A 32-year-old Saudi man presented to KKUH neurology clinic in December 1986 with a 1-month history of headache and depressive mood. He was physically normal. Five weeks later, he was admitted with aggravation of his headache and blurring of vision. On examination he had bilateral papilledema and erythema nodosum-like lesions, which were found histologically to be thrombophlebitis of the lower limbs. Laboratory results are summarized in Table 1. The CT brain scan was normal. Transvenous DSA showed a filling defect in the posterior portion of the superior sagittal sinus. The patient's symptoms and signs improved with dexamethasone therapy. During follow-up the patient developed recurrent orogenital ulcers.

Case 3

A 26-year-old Syrian man was seen in his home country in May 1986 with a 2-week history of sudden onset of severe headache and visual deterioration. He was found to have bilateral papilledema.

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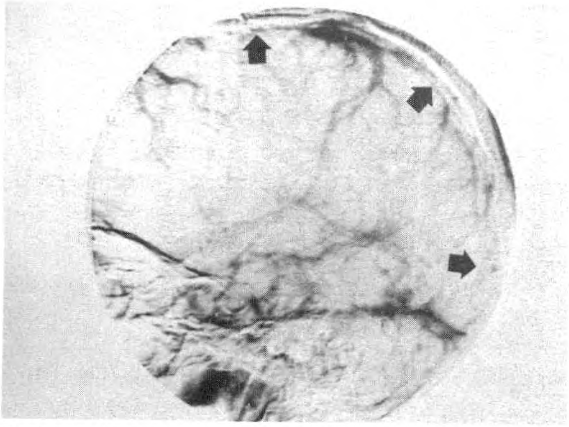

FIGURE 1. Case 1. Transvenous DSA showing almost complete nonvisualization of sagittal sinus and transverse venous sinuses.

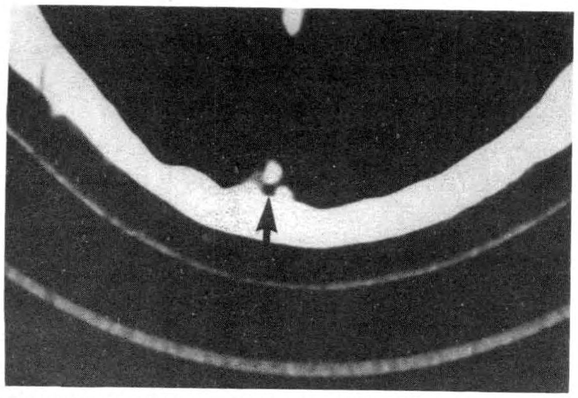

FIGURE 2. Case 1. CT scan following DSA indicates a thrombus within the torcular Herophili.

The CT brain scan was normal, and CSF examination revealed a pressure of 500 mm H_2O with normal cells and biochemistry. He was treated with dexamethasone and acetazolamide with a presumptive diagnosis of pseudotumor cerebri. His vision deteriorated despite insertion of a ventriculoperitoneal shunt in November 1986. Six months later, he was referred to KKUH with bilateral optic atrophy and visual acuities of 20/100 on the right and counting fingers only with the left eye. Results of laboratory investigations appear in Table 1.

A repeat CT brain scan and magnetic resonance imaging (MRI) were normal. The DSA through the right superficial femoral artery showed nonvisualization of the transverse sinus with abundance of collaterals. The patient received anticoagulant therapy and was discharged. Three weeks later, he developed an aneurysm and thrombotic occlusion at the site of the arterial puncture (Figure 3). Aneurysmectomy, removal of the thrombus, and restoration of normal circulation with vein graft were performed. One week later, the right femoral artery ruptured and was repaired successfully. One month later, orogenital ulcers and severe headache developed. On examination, the patient had signs of meningeal irritation. His CSF findings were compatible with the diagnosis of aseptic meningitis (Table 1). The patient was treated with prednisolone, 60 mg daily, with improvement of his headache.

TABLE 1. *Laboratory findings.*

Clinical tests	Patient			
	1	2	3	4
Blood				
ESR (mm/h)	52	55	30	70
WBC ($\times 10^9$/L)	10.7	13.7	10	20
VDRL	Negative	Negative	Negative	Negative
Hb electrophoresis	Normal	Normal	Normal	Normal
Anti-DNA antibodies	Negative	Negative	Negative	Negative
HLA-B5	Positive	Positive	Negative	Positive
CSF				
Pressure (mm H_2O)	490	330	110	320
Leukocytes ($\times 10^6$/L)	10	Nil	100	Nil
Protein (g/L)	1.47	0.26	0.80	0.28
Glucose	Normal	Normal	Normal	Normal
Oligoclonal bands	Negative	Negative	Negative	Negative
Immunoglobulins	Elevated IgG	Elevated IgA	Normal	Not done

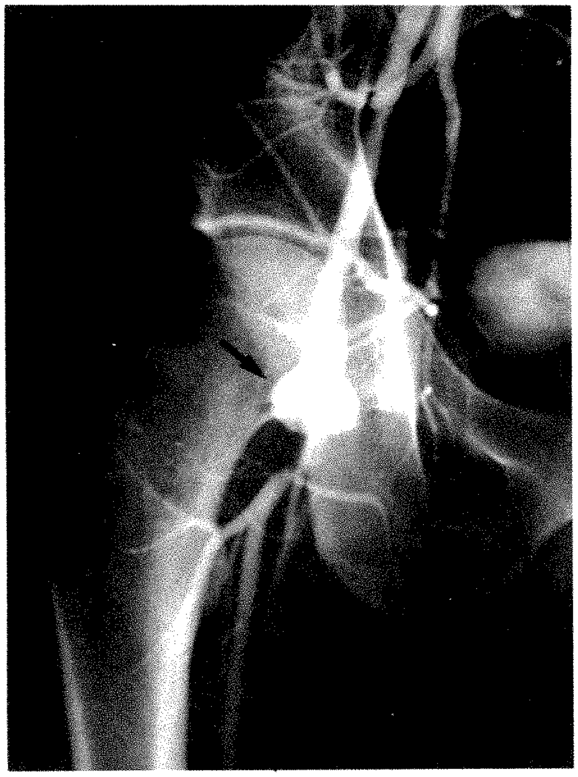

FIGURE 3. Case 3. Aneurysm of the superficial femoral artery.

Case 4

This 40-year-old Egyptian man who presented to KKUH with headache and blurring of vision of 2 weeks' duration was found to have bilateral papilledema. The patient gave a history of infrequently recurring aphthous ulcers for which he sought no medical advice. Results of laboratory investigations appear in Table 1. The brain CT scan was normal. Transvenous DSA showed partial occlusion of the superior sagittal sinus. The patient was put on dexamethasone and initially heparin and was discharged on dexamethasone and warfarin.

One month later, the patient was readmitted with thrombosis of the left popliteal vein and arthritis of the wrists, knees, and hips. The patient was put on heparin again, and while in the hospital, he developed fever, and *Staphylococcus aureus* was cultured from his blood. He received the appropriate antibiotics and was discharged in good condition with improvement in his papilledema and deep vein thrombosis and resolution of his arthritis.

Discussion

The diagnosis of Behcet's syndrome relies primarily on clinical criteria without specific laboratory findings including histopathologic confirmation. There are three main sets of criteria for the diagnosis of Behcet's syndrome: the Barnes criteria, the Shimizu criteria adopted by the Behcet's Syndrome Research Committee of Japan, and the O'Duffy criteria.[16] The O'Duffy criteria are based on the six most common clinical manifestations.[2] It requires that three of the following six criteria be present: (1) recurrent aphthous stomatitis, (2) genital aphthous ulcers, (3) uveitis, (4) synovitis, (5) cutaneous vasculitis, and (6) meningoencephalitis. According to O'Duffy's criteria, which have been adopted widely, our patients 2 and 3 satisfied the diagnosis of complete Behcet's syndrome, while cases 1 and 4 suffered from the incomplete syndrome.

A number of minor diagnostic criteria have also been defined based arbitrarily on the frequency with which they occur.[1,2] Papilledema is not included among these although it is well documented in Behcet's syndrome, and it may antedate the appearance of other symptoms and signs.[4,7,8,10,13,14] In reviewing large series, papilledema has been quoted variously as being found in 4.6%,[17] 9%,[18] 20%,[4] and 25%[7] of patients with neurologic manifestations, the frequency of the latter varying from 10% to as high as 49% of all cases.[1-4]

In view of this, we suggest that papilledema should be included among the minor diagnostic criteria for Behcet's syndrome. Certainly, it appears to be at least as common as some of the other less frequently encountered manifestations such as epididymitis, gastroenterological dysfunction, or cardiac involvement.[1,2] There may be ethnic variation in the incidence of papilledema in Behcet's disease. In an assessment of the ocular manifestations of Behcet's disease in 32 white American patients, papilledema was absent and disk swelling was found only in association with uveitis.[19] Three of our four patients are HLA-B5 positive, which is in agreement with the Japanese and Turkish findings of a significant increase in this histocompatibility antigen which has not been found in the West.[2] Sex and age seemed to influence the clinical expression of the disease.[20] All our patients who manifested papilledema as the initial manifestation of Behcet's disease were males.

In all four patients, papilledema was due to cerebral venous sinus thrombosis demonstrated by DSA (Figures 1 and 2). This has been reported as the underlying cause of brain swelling in Behcet's syndrome although some authors continue to ascribe this erroneously to benign intracranial hypertension.[20-22] It is worth noting that our cases 2 and 4 fulfilled the accepted criteria for benign intracranial hypertension[22] and would have been misdiagnosed if they had not been subjected to DSA and followed up regularly.

Spontaneous arterial aneurysm formation is relatively common in Behcet's syndrome.[3] This propensity for aneurysm formation may be augmented by arterial punctures as shown in one of our patients and two previous reports.[23,24] The result of surgery in such cases is uncertain, and the course is usually complicated, as demonstrated in our patient and in the literature.[23-25] Hence, we suggest that arterial punctures are to be avoided, and for visualization of the venous sinuses of the brain, the transvenous route for DSA is recommended. Recently, MRI has been proposed as a procedure of choice for the initial evaluation of dural sinus thrombosis,[26] which should be ideal in Behcet's syndrome where thrombophlebitis may develop after venous punctures.[27]

Conclusion

Dural venous sinus thrombosis was demonstrated in all four patients by DSA. Transarterial DSA performed in one patient resulted in postangiographic aneurysm and thrombosis at the site of puncture. We wish to propose the following:

1. Papilledema should be included as a separate minor criterion for diagnosis of Behcet's syndrome. It is often referred to as "benign intracranial hypertension,"[4,7,20-22,28] which is not correct as it is due to cerebral venous sinus thrombosis.
2. Transvenous DSA should be used for the investigation of patients with papilledema, as patients with Behcet's syndrome may be more prone to develop aneurysms after arterial punctures. Accordingly, angiography and transarterial DSA should be avoided if possible.
3. Behcet's syndrome should be suspected as a cause of papilledema, particularly in young male patients in areas where the disorder occurs.

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References

1. Shimizu T, Ehrlich GE, Inaba G, Hayashi K. Behcet disease (Behcet syndrome). Semin Arthritis Rheum 1979;8(4):223-60.
2. O'Duffy JD. Behcet's disease. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge C, eds. Textbook of rheumatology. Philadelphia: WB Saunders, 1981:1197-1202.
3. James DG, Spiteri MA. Behcet's disease. Ophthalmology 1982;89(11):1279-84.
4. Fadli ME, Youssef MM. Neuro-Behcet's syndrome in the United Arab Republic. Eur Neurol 1973;9:76-89.
5. Masheter HC. Behcet's syndrome complicated by intracranial thrombophlebitis. Proc R Soc Med 1959;52:1039-40.
6. Mounsey JPD. Oro-genital ulceration with phlebothrombosis (?Behcet's syndrome) complicated by osteomyelitis of lumbar spine and ruptured aorta. Br Med J 1965;1(5431):357-61.
7. Kalbian VV, Challis MT. Behcet's disease: report of 12 cases with three manifesting as papilledema. Am J Med 1970;49:823-9.
8. Bousser MG. Cerebral vein thrombosis in Behcet's syndrome (letter). Arch Neurol 1982;39:322.
9. Imaizumi M, Nukada T, Yoneda S, Abe H. Behcet's disease with sinus thrombosis and arteriovenous malformation in brain. J Neurol 1980;222(3):215-8.
10. Pamir MN, Kansu T, Erbengi A, Zileli T. Papilledema in Behcet's syndrome. Arch Neurol 1981;38(10):643-5.
11. Rosenberger A, Adler OB, Haim S. Radiological aspects of Behcet disease. Radiology 1982;144(2):261-4.
12. Segasothy M. Behcet's syndrome with sagittal sinus and inferior vena caval thrombophlebitis. Med J Malaysia 1982;37(2):132-3.
13. Ben-Itzhak J, Keren S, Simon J. Intracranial venous thrombosis in Behcet's syndrome. Neuroradiology 1985;27(5):450.
14. Bousser MG, Chiras J, Bories J, Castaigne P. Cerebral thrombosis: a review of 38 cases. Stroke 1985;16(2):199-213.
15. Harper CM Jr, O'Neill BP, O'Duffy JD. Intracranial hypertension in Behcet's disease: demonstration of sinus occlusion with use of digital subtraction angiography. Mayo Clin Proc 1985;60:419-22.
16. Jorizzo J. Behcet's disease: an update based on the 1985 International Conference in London. Arch Dermatol 1986;122(5):556-8.
17. Wolf SM, Schotland DL, Phillips LL. Involvement of nervous system in Behcet's syndrome. Arch Neurol 1965;12:315-25.
18. Kawakita H, Nishimura M, Satoh Y, Shibata N. Neurological aspects of Behcet's disease: a case report and clinico-pathological review of the literature in Japan. J Neurol Sci 1967;5:417-39.

19. Colvard DM, Robertson DM, O'Duffy JD. The ocular manifestations of Behcet's disease. Arch Ophthalmol 1977;95(10):1813-7.
20. Yazici H, Tuzun Y, Pazarli H, et al. Influence of age of onset and patients' sex on the prevalence and severity of manifestations of Behcet's syndrome. Ann Rheum Dis 1984;43(6):783-9.
21. Graham EM, Al-Ashkar AF, Sanders MD, Hilton P. Benign intracranial hypertension in Behcet's syndrome. Neuro-ophthalmology 1980;1:73-6.
22. Miller NR. Benign intracranial hypertension: the pseudotumor cerebri syndrome. In: Walsh FB, Hoyt WF, eds. Clinical neuro-ophthalmology, vol 1. Baltimore: Williams and Wilkins, 1982:199-211.
23. Kingston M, Ratcliffe JR, Alltree M, Merendino KA. Aneurysm after arterial puncture in Behcet's disease. Br Med J 1979;1(6180):1766-7.
24. Rae SA, Vandenburg M, Scholtz CL. Aortic regurgitation and false aortic aneurysm formation in Behcet's disease. Postgrad Med J 1980;56(656):438-9.
25. Jenkins AM, Macpherson AI, Nolan B, et al. Peripheral aneurysms in Behcet's disease. Br J Surg 1976;63(3):199-202.
26. Purvin V, Dunn DW, Edwards M. MRI and cerebral venous thrombosis. Comput Radiol 1987;11(2):75-9.
27. Chajek T, Fainaru M. Behcet's disease: a report of 41 cases and a review of the literature. Medicine 1975;54(3):179-96.
28. Mechelson JB, Chisari FV. Behcet's disease. Surv Ophthalmol 1982;26(4):190-203.

PHEOCHROMOCYTOMA ASSOCIATED WITH PREGNANCY: A CASE REPORT

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Pheochromocytoma is a rare cause of hypertension, occurring very infrequently during pregnancy. Only in a third of the reported cases was an antepartum diagnosis made. When antepartum diagnosis is made, critical monitoring of the blood pressure and its control with alpha-adrenergic blockers during pregnancy and delivery, delivery of the fetus at term by cesarean section followed by surgical extirpation of the tumor in a single operation are the factors conducive to lowering the fetal and maternal mortality in such cases.

Case Report

A 32-year-old Palestinian woman, gravida 4, para 3 + 0, was referred from Nasariya Health Center at 30 weeks' pregnancy. She had paroxysmal attacks of headaches, sweating, palpitations, and dizziness as well as occasional fainting unrelated to any specific activity. A provisional clinical and ultrasound diagnosis of pheochromocytoma had been made. Her three previous pregnancies had been normal.

The only contributory medical history was that 2 years previously, she was found to be hypertensive prior to an external ear operation and treated successfully with labetalol for 3 days. However, after the operation and discharge from the hospital, she had an incidence of shock.

In view of the provisional diagnosis of pheochromocytoma, she was admitted to the hospital. Her blood pressure was 170/100 mm Hg, with a regular pulse rate of 80 beats per minute. Her previous symptoms of paroxysmal attacks of headaches, flushing, and dizziness continued, and the blood pressure was very labile, ranging from 80/60 to 220/100 mm Hg regardless of the increased dosage of labetalol, 100 mg three times a day. An electrocardiogram showed sinus tachycardia at a rate of 100 beats per minute and left ventricular hypertrophy.

Biochemical investigations revealed significantly elevated 24-hour urinary vanillylmandelic acid (VMA) and catecholamines (Table 1). The urea, electrolytes, uric acid, and creatine clearance levels were normal. However, her liver function tests showed elevated enzymes (Table 1). The hemoglobin was 86 g/L after ferrous gluconate, folic acid, and vitamin C supplement therapy. The coagulation profile was normal.

Pregnancy screening tests were normal. The hepatitis surface antigen test was nonreactive.

TABLE 1. *Summary of biochemical results.*

24-hour urinary VMA
- 198.8 μmol/d
- 148.8 μmol/d
- 195.9 μmol/d
- (normal, up to 40 μmol/d)

Catecholamines
- Noradrenaline: 2500 μmol/d (normal, up to 40 μmol/d)
- Adrenaline: 390 μmol/d (normal, up to 18 μmol/d)

Liver function tests
- Total bilirubin: 33 μmol/L (normal, up to 17 μmol/L)
- Direct bilirubin: 14 μmol/L (normal, up to 4.5 μmol/L)
- Alkaline phosphatase: 387 U/L (normal, up to 53 U/L)
- Alanine aminotransferase: 281 U/L (normal, up to 53 U/L)
- Aspartate aminotransferase: 535 U/L (normal, up to 40 U/L)

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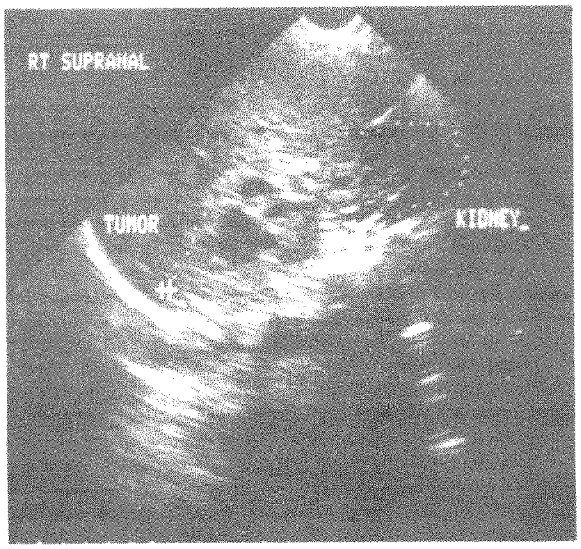

FIGURE 1. Abdominal sonogram showing multicystic lesions in relation to the upper pole of the right kidney.

She was placed on normal diet, normal salt intake, and complete bedrest, and her hypertension was controlled with labetalol, 100 mg three times a day.

Ultrasound scan of the abdomen showed a normal fetus with an estimated weight of 2.5 ± 0.5 kg, an estimated gestational age of 30, 32, and 34 weeks by biparietal diameter, femur length, and abdominal circumference measurements, respectively. The ultrasound scan also revealed a multiloculated mass of 5 × 6 × 8 cm with solid and cystic components in the region of the upper pole of the right kidney. The left kidney and suprarenal region were normal, other than a 1.1-cm-long renal calculus in the lower renal pole (Figure 1). No evidence of secondary tumors was seen in the liver, nor was infiltration noted in the inferior vena cava.

The patient was cross-matched for 6 units of whole blood, 4 units of fresh-frozen plasma, and 10 units of platelets. At 34 weeks' gestation, she was operated on by a combined team of a general surgeon and obstetrician. Central venous and arterial lines were secured, and general anesthesia was induced with thiopental and maintained with nitrous oxide and oxygen, halothane, and atracurium. An elective lower segment cesarean section was performed through a vertical subumbilical incision. A live female baby, 2.480 kg in weight, and with Apgar scores of 7 and 8 was delivered. The mother was given fentanyl after the delivery of the fetus. Blood pressure was controlled with phentolamine and nitroprusside infusion whenever it rose sharply.

Following the delivery of the baby, the subumbilical incision was extended into the right hypochondrium. A complete excision of a large hemorrhagic suprarenal tumor 4.5 cm in diameter and with solid and cystic components was performed. A liver biopsy specimen was taken and was normal. Exploration of the entire abdomen showed no other abnormality or evidence of metastasis.

During excision of the tumor, the blood pressure rose to 250/115 mm Hg during palpation of tumor and was controlled within 1 minute with a bolus injection of phentolamine. The total blood loss was 2500 mL, and she was transfused with 4 units of whole blood. Dextrose-saline, Ringer's lactate, and oxytocin infusion were also administered during the operation. Blood glucose was monitored repeatedly to avoid hypoglycemia.

Her postoperative condition was satisfactory with a blood pressure of 150/90 mm Hg. Postoperatively the VMA levels returned to normal, being 34, 24 and 18 μmol/d on three occasions. She was placed on labetalol 100 mg once daily. Her postoperative recovery was uneventful and she was discharged on the 10th postoperative day. The baby made satisfactory progress in the neonatal intensive care unit where she was kept due to prematurity.

Follow-up of the mother at the postnatal and surgical clinics showed satisfactory progress. Her blood pressure remained in the range of 90/60 mm Hg for months. She became symptom-free, and all medications were discontinued.

Discussion

Pheochromocytoma, a tumor of the chromaffin cells of the adrenal medulla system, occurs in about 0.1% of routine autopsy specimens.[1] The tumor occurs at any age, being commonest in the fourth and fifth decades with a slight predilection for women.[1] Its occurrence during pregnancy has been documented in about 128 cases.[2-9] In only slightly over one third of these was antepartum diagnosis made.[1-9] Cases have also been reported complicating the immediate puerperium.[10]

The clinical symptoms of pheochromocytoma are numerous and diverse and are mainly due to the pharmacologic effects of excess circulating catecholamines or the complications of hypertension induced by these pressor amines. Hence, paroxysmal attacks of headaches, hyperhydrosis, palpitations, anxiety syncope with paroxysmal and/or labile hypertension are the commonest features in over 75%.[1] These attacks become more frequent and severe with the passage of time. The attacks may be precipitated by a variety of factors, such as massage or pressure on the tumor by postural changes or a sudden rise in abdominal pressure as occurs in laughing and straining at stool. Ingestion of certain foods containing tyramine or synephrine, such as wine, cheese, or citrus food, may precipitate an attack, and is a known cause as well. The condition may present as adult respiratory distress syndrome in pregnancy.[2]

In pregnancy, abdominal palpitation and changes of posture during medical examination and sexual intercourse are known to provoke a crisis.[1] Such symptoms as well as paroxysmal or sustained hypertension of unknown cause or recent occurrence must be evaluated for the presence of pheochromocytoma and must be differentiated from eclampsia or pre-eclampsia in which the hypertension is nonlabile. Pheochromocytoma must also be borne in mind when shock occurs during or immediately after labor.[3] Previous history, ultrasound screening, and VMA measurements would easily identify the presence of pheochromocytoma if present.

Ten percent of pheochromocytoma cases are familial, and 10% occur in association with other endocrine lesions, such as multiple endocrine neoplasia (Sipple's syndrome).[11,12] Sipple's syndrome in pregnancy is rare. Only two such cases have been reported. As such, hypertension patients with a diagnosis of pheochromocytoma in a kindred or with uncontrollable diabetes in pregnancy must be screened for pheochromocytoma.

Diagnosis

Antepartum diagnosis is mandatory in pregnancy as this reduces maternal mortality from 58% to 18% and fetal mortality from 50% to 18%.[13] Confirmation of the clinical diagnosis can be made by the estimation of the urinary catecholamines or their metabolites which are invariably elevated. Quantification of serum and urinary epinephrine and norepinephrine is also advised, as they may be elevated in patients with multiple endocrine neoplasia in the presence of normal catecholamines.[1] This is the most sensitive biochemical test for pheochromocytoma and was used in the patient described here.

Other diagnostic approaches including nephrotomography, angiography, computed tomography, and scintigraphy using ^{131}I metaiodobenzylgandine accurately and graphically demonstrate the lesions. Furthermore, they readily demonstrate the location of the tumors, which are 70% bilateral, 10% multiple, and 10% extra-adrenal in site.[8]

All these tests have radiation hazards, however, and should be avoided in pregnancy. Hence, they were not used in this case. Moreover, scintigraphic scan is not readily available. Furthermore, contrast media used in these examinations interfere with the measurement of catecholamines by lowering their values. Serum catecholamines should be measured before or at least 3 days after diagnostic examinations in which contrast media are used.[1]

Ultrasound scan is the diagnostic tool of choice for confirming suspected cases of pheochromocytoma. It has no radiation hazards, can be repeated as often as needed, and carries no interventional risks. Above all, it is a diagnostic tool readily available. Hence, it was used in this case. Not only did it demonstrate the lesion, it offered a clue to its size, its consistency, and its unifocal site. Furthermore, the ultrasound scan must include an assessment of the fetal abdomen, since fetal neuroblastoma can produce increased urinary catecholamines in pregnancy.[1]

Magnetic resonance imaging is the latest modality used successfully in diagnosis, and it is hazard free.[14] It should therefore be used whenever available.

Management

Pheochromocytoma occurring during the first and third trimesters of pregnancy should have immediate surgical extirpation of the tumor, though its excision may precipitate abortion of the fetus during the first trimester. During the third trimester, elective cesarean section combined with surgical excision of the tumor should be undertaken in one operation as was done in this case,[3] thus drastically reducing maternal and fetal mortalities.[2-8] Labor and vaginal delivery must be avoided, as these procedures induce physical and emotional stresses which provoke hypertensive crises in these patients with resultant increased maternal and fetal wastage, even though a recent report documents a case successfully managed by vaginal delivery under epidural anesthesia.[15]

Patients in the second trimester may be brought to term under adequate treatment with an alpha-receptor blocking agent, after which the patient is treated as a third trimester case.[8]

At surgery, subumbilical incision is preferred for the cesarean section, and this incision is extended upward for the extirpation of tumor.[3,9,16] This was the procedure followed in this case.

The routine use of phenoxybenzamine in the control of the patient's blood pressure until the patient is brought to term has been widely advocated.[2,3,8] However, some have successfully used a combination of alpha-adrenergic and beta-adrenergic blockade with dopamine synthesis inhibitors.[17] In this case, the patient was maintained on labetalol, which is an alpha- and beta-blocking agent.

The cornerstone to successful surgery in patients with a pheochromocytoma is the preoperative and operative medical control of the cardiovascular responses to high levels of circulating catecholamines with alpha-blockers such as phenoxybenzamine and beta-blocking drugs if dysrhythmias are present.[18] The vital signs, including arterial and pulmonary pressures, are thus critically monitored during surgery.[17] General anesthesia is usual for such patients, and induction is achieved by thiopental and succinylcholine chloride and is maintained by nitrous oxide, oxygen, and halothane.[5,19] Rapid tracheal intubation during general anesthesia is suggested, though it may induce reflex sympathoadrenal response with consequential rise in maternal blood pressure, hence the need for prophylactic intravenous infusion of phentolamine and vocal cord anesthesia with topical lidocaine. Intravenous infusion of phentolamine is continued during surgery to prevent any sudden rise in the blood pressure, especially during palpation and removal of the fetus.

Spinal analgesia has been used but is not advised. It may be associated with a precipitous fall in blood pressure, the level of anesthesia cannot be well controlled, nor can the anesthesia be prolonged once established.[20] However, continuous epidural analgesia can also be used, and some have advocated this due to its advantages which include the simplicity of the technique and the avoidance of maternal aspiration.[9]

References

1. Manager WM, Gifford RW Jr, Hoffman BB. Pheochromocytoma: a clinical and experimental overview. Curr Prob Cancer 1985;9(5):5-89.
2. Feldman JM. Adult respiratory distress syndrome in a pregnant patient with pheochromocytoma. J Surg Oncol 1985;29(1):5-7.
3. Fudge TL, McKinnon WM, Geary WL. Current surgical management of pheochromocytoma during pregnancy. Arch Surg 1980;115(10):1224-5.
4. Oishi S, Shimada T, Inoue J, Sato T. Pheochromocytoma associated with pregnancy: a case report and review of 22 cases in Japanese literature. Nippon Naika Gakkai Zasshi 1985;74(4):467-72.
5. Pinaud M, Michel J, Arnould F, et al. Association pheochromocytome surrenalien bilateral et grossesse: cesarienne et surrenalectomies simultanees. Can Anesthesiol 1985;33(4):321-4.
6. Pinaud M, Souron R, Le Neel JC, et al. Bilateral phaeochromocytoma in pregnancy: anaesthetic management of combined caesarean section and tumour removal. Eur J Anaesthesiol 1985;2(4):395-9.
7. Stanley JH, Sanchez F, Frey GD, Schabel SI. Computed tomography evaluation of pheochromocytoma in pregnancy. J Comput Tomog 1985;9(4):369-72.
8. Stenstrom G, Swolin K. Phaeochromocytoma in pregnancy: experience of treatment with phenoxybenzamine in three cases. Acta Obstet Gynaecol Scand 1985;64(4):357-61.
9. Stonham J, Wakefield C. Phaeochromocytoma in pregnancy: caesarean section under epidural analgesia. Anaesthesia 1983;38(7):654-8.
10. Epstein H, Morehouse M, Cowles T, King CR. MEA III presenting as pheochromocytoma and complicating pregnancy and the puerperium: a case report. J Reprod Med 1985;30(6):501-4.
11. Chodankar CM, Abhyankar SC, Deodhar DP, Shanbhag AM. Sipple's syndrome (multiple endocrine neoplasia) in pregnancy: case report. Aust NZ J Obstet Gynaecol 1982;22(4):243-4.
12. Gilstrap LC, Brekken AL, Harris RE. Sipple syndrome and pregnancy. JAMA 1976;235(11):1136-7.
13. Schenker JG, Chowers I. Pheochromocytoma and pregnancy: review of 89 cases. Obstet Gynecol Surv 1971;26:739-47.
14. Greenberg M, Moawad AH, Wieties BM, et al. Extra-adrenal pheochromocytoma: detection during pregnancy using MR imaging. Radiology 1986;161(2):475-6.
15. Davies AE, Navaratnarajah M. Vaginal delivery in a patient with a phaeochromocytoma: a case report. Br J Anaesth 1984;56(8):913-6.

16. Leak D, Carroll JJ, Robinson DC, Ashworth EJ. Management of pheochromocytoma during pregnancy. Obstet Gynecol Surv 1977;32(7):583-5.
17. Devoe LD, O'Dell BE, Castillo RA, et al. Metastatic pheochromocytoma in pregnancy and fetal biophysical assessment after maternal administration of alpha-adrenergic, beta-adrenergic, and dopamine antagonists. Obstet Gynecol 1986;68(3 suppl):15S-18S.
18. Burgess GE 3d. Alpha blockade and surgical intervention of pheochromocytoma in pregnancy. Obstet Gynecol 1979;53(2):266-70.
19. Smith AM. Phaeochromocytoma and pregnancy. J Obstet Gynaceol Br Commonw 1973;80:848-51.
20. Bromage PR, Millar RA. Epidural blockage and circulatory catecholamine levels in a child with phaeochromocytoma. Can Anaesth Soc J 1958:281-7.

CHILDHOOD CHRONIC RELAPSING INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: DRAMATIC AND LONG-LASTING RESPONSE TO PLASMA EXCHANGE

Tahir Obeid, MRCP; Generoso Gascon, MD; Karl E. Astrom, MD, PhD

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a human disease with a slow onset and a course which is either steadily progressive or relapsing and remitting.[1] It is probably caused by immunologic disturbances. Both cellular and humoral factors are involved.[1,2] The possible presence of a humoral pathogenic factor is the rationale for using plasma exchange as treatment.[1-11] Only one prospective double-blind study[11] has assessed the efficacy of plasma exchange. Statistically significant improvement in neurologic functions and increased nerve conduction velocity in some patients ("responders") occurred.

We describe a child with CIDP in whom plasma exchange was followed by rapid and long-lasting improvement of muscle power.

Case Report

A healthy 3-year-old Lebanese boy without family history of neurologic and skeletomuscular diseases slowly developed weakness in his arms and legs after a mild upper respiratory tract infection. He was admitted to King Khalid University Hospital (KKUH) on 3 November 1984, 45 days after the beginning of the disease. On examination he appeared to be healthy but was hypotonic and weak in the arms and legs (grade 2-3 on the MCR scale). Deep tendon reflexes were absent. Mental status, cranial nerves, and all sensory examinations were normal. He exhibited no respiratory distress or skeletal abnormalities. Cerebrospinal fluid examination showed 4 cells and 0.96 g/L of protein (reference range, 0.20 to 0.45 g/L). He had normal blood cell counts and biochemical findings. Motor conduction velocity was slow (10 to 15 meters/second) in the median, ulnar, and tibial nerves, and the action potentials could not be obtained in the sensory nerves. The diagnosis was acute inflammatory demyelinating polyradiculoneuropathy (the Guillain-Barre syndrome). After discharge, the child gradually improved and eventually regained about 70% of his original motor strength without drug therapy but only physiotherapy. Motor nerve conduction velocities remained slow (12 to 18 meters/second) on the same sampled nerves (Figure 1), and tendon reflexes were absent on follow-up.

Following an upper respiratory tract infection 14 months after the initial episode, the patient again developed weakness and was admitted to KKUH on 22 February 1986. He had profound weakness in his arms and legs (power grade 1) and was bedridden. Sensation were normal, but tendon reflexes were absent. Peripheral nerves were not enlarged. The CSF examination showed protein of 0.90 g/L, no cells, and a normal CSF index. Oligoclonal bands were not found. Examinations for metabolic, endocrine, and collagen diseases were negative. Serum lead and arsenic levels were normal. Neurophysiologic examination showed slow motor conduction velocity in the median, ulnar, and tibial nerves (10 to 16 meters/second) and absence of action potentials in sensory nerves. The F-wave responses supported the diagnosis of polyradiculoneuropathy. A sural nerve biopsy showed decreased number of myelinated fibers (not quantitated), demyelination, onion bulbs, and a few monocytic cells in the endoneural connective tissue (Figures 2 and 3).

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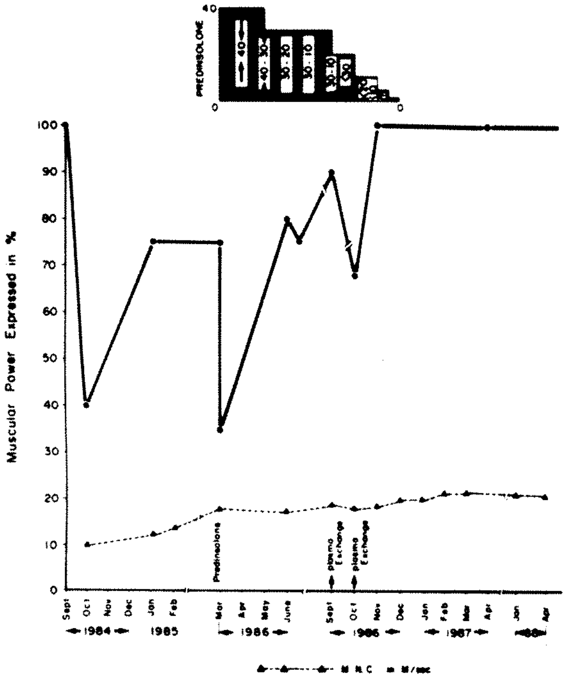

FIGURE 1. The patient's muscular power (solid line) tested in the deltoid and quadriceps muscles and the hand grip in response to prednisolone and plasma exchange. The muscular power showed a dramatic and immediate response to plasma exchange with prolonged remission after the second series of plasma exchanges. The motor nerve conduction studies (MNC expressed in meters per second) showed very little corresponding improvement.

At this point the diagnosis was changed to CIDP, and the patient was given prednisolone starting with 40 mg daily with very gradual tapering until the dose was 30 mg alternating with 10 mg on a daily basis. This was the effective dose to maintain a reasonable power, and he was able to walk after 2 months and eventually regained about 80% of his normal motor strength. After medication with steroids for 6 months, cushingoid features appeared. We considered immunosuppressive drugs or plasma exchange, but the patient's father wanted a second medical opinion. The diagnosis of CIDP was confirmed at the Mayo Clinic in the United States, and a trial with plasma exchange was suggested.

After his return to Saudi Arabia in August 1986, the patient had 6 sessions of plasma exchange over 3 weeks. In each session, 800 mL of the patient's plasma was removed and replaced by human protein over a period of 60 to 90 minutes. A few hours after each session, dramatic improvement occurred. At the end of this treatment, he had regained about 90% of his normal muscle power. Six weeks later after an influenza-like illness, the boy again developed generalized muscle weakness. Treatment with plasma exchange, four sessions during 4 weeks, again resulted in drama-

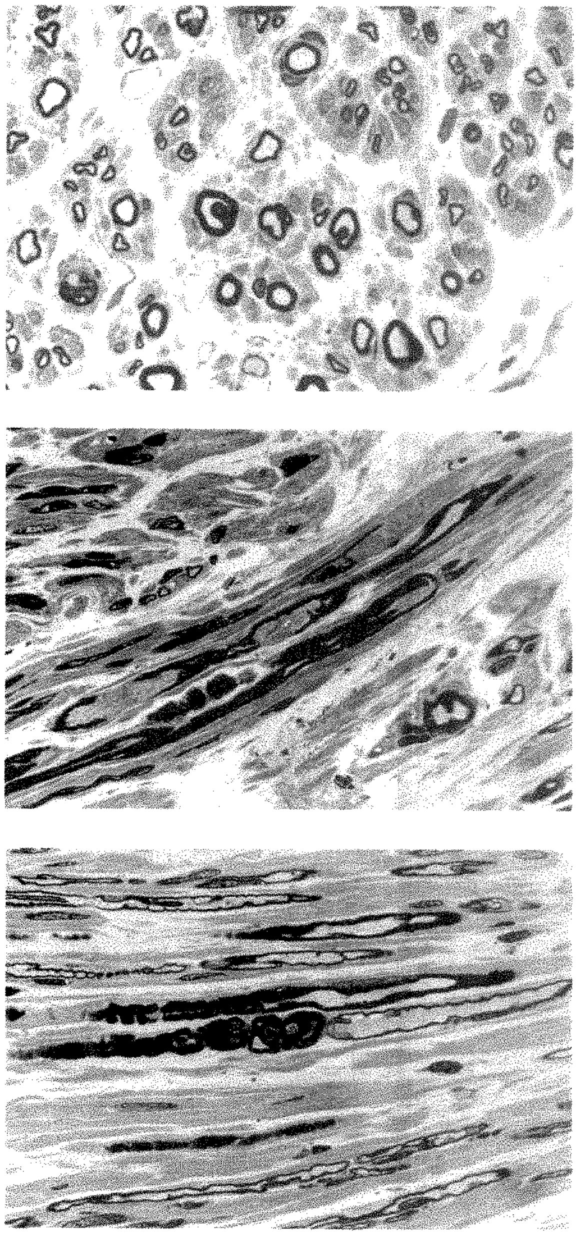

FIGURE 2. Top, cross-section of sural nerve shows onion bulb (upper right) and degeneration of myelin (left edge). Center, longitudinal sections show segmental demyelination. Bottom, segment with thin sheath of myelin at node of Ranvier indicates remyelination (epoxy-resin-embedded sections, original magnification, ×500).

tic improvement. Treatment was ended on 30 October 1986. Since then, the patient has had full muscle power without steroids for 20 months. There has been no muscle wasting. Tendon reflexes have remained absent, and nerve conduction velocities increased very little in the median, ulnar, and tibial nerves (16 to 22 meters/second) (Figure 1). All the neurophysiologic studies were standardized in the sense that they were carried out by the same examiner using the same equipment.

Discussion

Our patient satisfied the diagnostic criteria for CIDP,[1,2,13] namely (1) a symmetrical

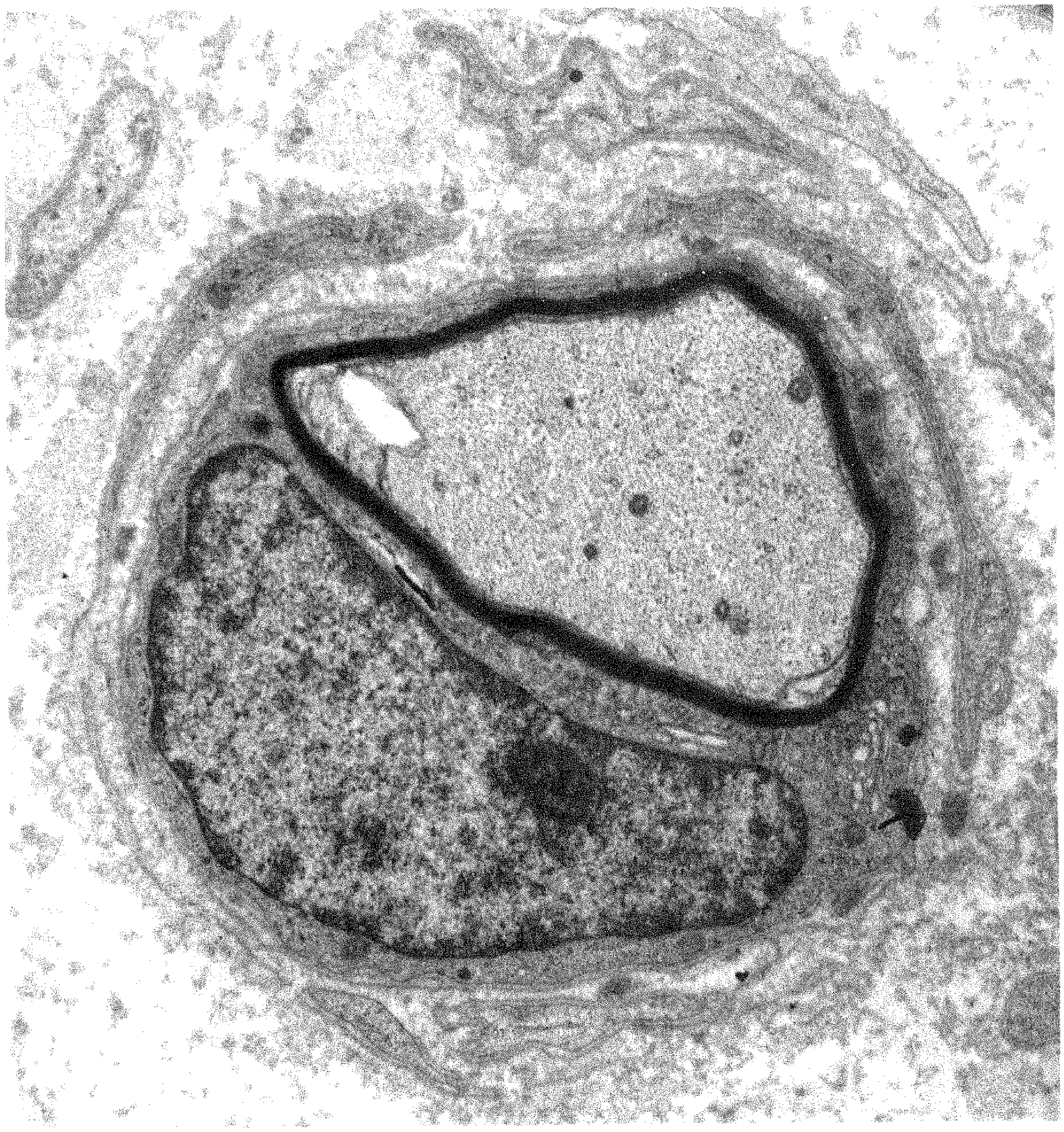

FIGURE 3. Electron micrograph of onion bulb in the sural nerve. Sheath of myelin is thin in relation to diameter of axon, which indicates remyelination (original magnification, × 12,000).

polyradiculoneuropathy; (2) a tendency toward involvement of proximal limb segments, less often trunk and only occasionally cranial nerves; (3) an elevated CSF protein level without cells, the so-called cytoalbumin dissociation; (4) nerve conduction and electromyographic alterations characteristic of a demyelinating neuropathy, with many instances of superimposed axonal degeneration; (5) inflammatory cell infiltrates, segmental demyelination, and axonal degeneration in spinal roots and peripheral nerves with or without the pathologic features of hypertrophic neuropathy; and (6) no other explanation for the neuropathy.

Several unusual features were noted in this case. First, each of the three episodes of weakness followed an influenza-like illness. A preceding viral illness is commonly noted in the acute Guillain-Barre syndrome but not in the chronic form.[1] Second, the patient regained his muscular power after treatment with steroids and plasma exchange, but the deep tendon reflexes remained absent and electrophysiologic examinations showed repeatedly depression of nerve function (Figure 1). Third, dramatic improvement occurred within hours of each plasma exchange treatment. Dramatic and rapid improvement may be an important favorable prognostic sign of long-lasting and full recovery. Finally, more than 20 months after treatment with plasma exchange, the patient has full muscle power. In the series of Dyck et al,[11] "improvement" began to disappear 10 to 14 days after treatment with plasma exchange. This may suggest that children have a better response to repeated plasma exchange than adults, probably due to disturbance in humoral more than cellular immunity. McCombe and colleagues found recently that CIPD in children has a good chance of recovery, and it is commonly responsive to steroid treatment.[14]

This rapid improvement after each session of plasma exchange confirms the efficacy of this method.[11] It supports the notion that muscle weakness, at least in part, is caused by a circulating factor or factors which can produce reversible blocks in axons of roots and peripheral nerves and is not caused by demyelination per se.[2]

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References

1. Dyck PJ, Arnason BJW. Chronic inflammatory demyelinating polyradiculoneuropathy. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy, 2nd ed. Philadelphia: WB Saunders, 1984:2101-14.
2. Dalakas MC, Engel WK. Chronic relapsing (dysimmune) polyneuropathy: pathogenesis and treatment. Appl Neurol 1981;9(suppl):134-45.
3. Pollard JD, McLeod JG, Gatenby P, Kronenberg H. Prediction of response to plasma exchange in chronic relapsing polyneuropathy: a clinico-pathological correlation. J Neurol Sci 1983;58(2):269-87.
4. Gross ML, Legg NJ, Lockwood MC, Pallis C. The treatment of inflammatory polyneuropathy by plasma exchange. J Neurol Neurosurg Psychiatry 1982;45(8):675-9.
5. Gross ML, Thomas PK. The treatment of chronic relapsing and chronic progressive idiopathic inflammatory polyneuropathy by plasma exchange. J Neurol Sci 1981;52(1):69-78.
6. Toyka KV, Augspach R, Wietholter H, et al. Plasma exchange in chronic inflammatory polyneuropathy: evidence suggestive of a pathogenic humoral factor. Muscle Nerve 1982;5(6):479-84.
7. Connor RK, Ziter FA, Anstall HB. Childhood chronic relapsing polyneuropathy: dramatic improvements following plasmapheresis. J Clin Apheresis 1982;1:46-9.
8. van Nunen SA, Gatenby PA, Pollard JD, et al. Specificity of plasmapheresis in the treatment of chronic relapsing polyneuropathy. Aust NZ J Med 1982;12(1):81-4.
9. Levy RL, Newkirk R, Ochoa J. Treating chronic relapsing Guillain-Barre syndrome by plasma exchange (letter). Lancet 1979;2(8136):259-60.
10. Server AC, Lefkowith J, Braine H, McKhann GM. Treatment of chronic relapsing inflammatory polyradiculoneuropathy by plasma exchange. Ann Neurol 1979;6(3):258-61.
11. Dyck PJ, Daube J, O'Brien P, et al. Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Engl J Med 1986;314(8):461-5.
12. Dyck PJ, Lais AC, Ohta M, et al. Chronic inflammatory polyradiculoneuropathy. Mayo Clin Proc 1975;50(11):621-37.
13. Prineas JW, McLeod JG. Chronic relapsing polyneuritis. J Neurol Sci 1976;27(4):427-58.
14. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy: a clinical and electrophysiological study of 92 cases. Brain 1987;110(pt 6):1617-30.

STRUCTURAL ABNORMALITIES OF THE Y CHROMOSOME ASSOCIATED WITH HYPOSPADIAS, INFERTILITY, AND SHORT STATURE

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The precise role of the Y chromosome or the gene(s) on the Y chromosome in the differentiation of the gonad (testis) is well established. To determine the phenotype-karyotype correlations, a number of cases with structural aberrations (deletions, translocations) of Y chromosome with varying degrees of clinical manifestations have been described. However, a direct correlation of the phenotype-karyotype presents disadvantages in cases of mosaicism and unusual multiple structural aberrations of the Y chromosome. Several cases of Y chromosomal abnormalities reported have suggested that one or more genes on the Y chromosome induce the undifferentiated gonad to develop into a testis; subsequent development is controlled by the action of hormones.

Recently the gene(s) responsible for male determination has been located at the middle third of the Y short arm.[1] Our aim here is to report on a rare case with unusual structural Y abnormalities and discuss its clinical significance.

Case Report

A 33-year-old Arab man was investigated for primary infertility after 9 years of marriage. Family history was unremarkable. He was one of twins (his twin brother died soon after birth). His first seminal emission was at the age of 15. He had penile hypospadias for which surgical correction was carried out.

Physical examination showed a masculine habitus, weighing 78 kg, 148 cm in height, and 157 cm in span. He showed mild facial asymmetry with diverted nasal bridge and short neck, facial and body hair was normal male type, and there was no gynecomastia. He showed normal phallus with urethral opening situated below the glans. Testes were small (5 ml), beaded, and firm. Semen analysis showed azoospermia.

Hormone profile indicated primary gonadal failure. The values were luteinizing hormone, 11.0 IU/L (normal, 2.2 to 12.0 IU/L); follicle stimulating hormone, 18.4 IU/L (0.9 to 9.8 IU/d); prolactin, 284 mIU/L (60 to 380 mIU/L); and testosterone, 12.0 nmol/L (10.5 to 35.0 nmol/L).

The patient refused gonadal biopsy. Skeletal radiographs and ultrasonography of the abdominal organs and pelvis showed no abnormalities.

Chromosomal analysis of 470 metaphase spreads using GTC, QFQ, and C-NaOH banding techniques revealed a variety of Y-chromosome configurations in variable percentages with normal 46,XY and 45,X cell lines (Table 1). Two cells with 47 chromosomes, one with two t(Yp;Yq) and the other with two del(Yq) were also found. Dicentric Y chromosome interpreted as 46,X, dic(Y) (Yqter-cen-Yp11.2::Yp11.2-cen-Yqter) (Figure 1a) has likely arisen from two Y chromosomes after the breakage and subsequent reunion of both at Yp11.2 bands. The submetacentric monocentric (Y) interpreted as t(Yp;Yq) is possibly the reunion of two Y chromosomes, one being deleted at Yp11.2 and the other at the Yq11.2 band (Yqter-cen-Yp11.2::Yq11.22-Yqter) (Figure 1c and c′). Two configurations of ring(Y) were observed, such as monocentric r(Y) (Figure

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TABLE 1. *Distribution of different cell types in blood lymphocyte culture of the proband.*

Type of cells	No.(%)
45,X	242(51.5)
46,XY	19(4.0)
46,X,del(Yq)	20(4.2)
46,X,t(Yp;Yq)	158(33.6)
46,X,dic(Y)	17(3.6)
46,X,r(Y)	12(2.5)
47,X,t(Yp;Yq),+t(Yp;Yq)	1(0.2)
47,X,del(Yq),+del(Yq)	1(0.2)
Total	470

1d) and dic r(Y) (Figure 1e). A small centric fragment was found in 4.2% of metaphases. This could be the deleted portion of Y(Ypter-cen-Yq11.22) (Figure 1f). Normal Y morphology is shown in Figure 1b. In Figure 2, C banding demonstrates very clearly the dic(Y) is symmetric with two centromeres, and t(Yp;Yq) is asymmetric and monocentric. Karyotype of the proband's elder brother was normal 46,XY, thereby indicating that the Y-chromosome abnormalities in the proband had arisen de novo.

Discussion

Different types of structural abnormalities of the Y chromosome, with or without 45,X cell line, in infertile males have been described.[2,3] The origin of various cell lines could be attributed to postzygotic events of chromosome breakage, nondisjunction, and somatic recombination.[4] The presence of 46,XY cell line in our case confirms the postzygotic nondisjunction events as the cause for structural rearrangements. Recently, Hiraishi et al[5] have discussed the origin of the structural abnormalities in connection with "normal" 46,XY cell line in an intersex girl. Their hypothesis was that the somatic recombination/sister chromatid exchange within a ring structure of the dicentric chromosome produces the "normal" Y chromosome (see Figure 2 dicY of our case). In such an

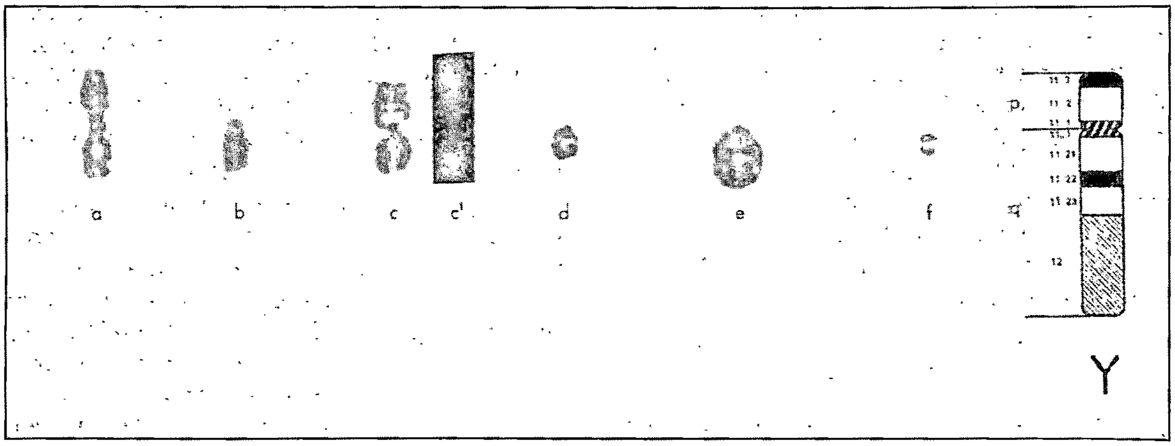

FIGURE 1. Morphology of the different Y chromosomes in G banding except c' (Q-banding).

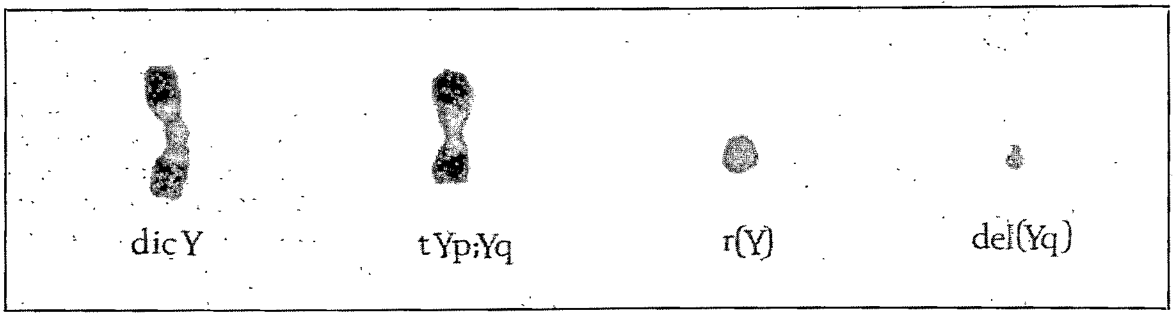

FIGURE 2. C-banding.

instance, the "normal" Y chromosome should have a deletion of the short arm terminal portion, very small to be visually detectable and testable by suitable DNA probes.

Similar to the two cases reported by Fryns et al,[4] the phenotype of our patient is perfectly male, though female sexual differentiation has been observed by some authors.[6-8] Clinical manifestations such as short stature and hypospadias are not uncommon in cases of Y-chromosome deletions.[6,9-11] It has been established that the male inducing/determining factor or the locus (loci) is at the Yp11 band.[2,3,12] In our patient, this band was intact, which was responsible for the male phenotype. The presence of different cell lines does not seem to have a major effect on the phenotype, except for the short stature, which could be due to considerable proportion of cells with 45,X, a feature consistent with Turner syndrome. Duplication of the heterochromatic region (Yq) does not show any unusual clinical manifestation unlike Yp duplication. However, the etiologic factors for infertility in structural aberrations of the Y chromosome with "normal" 46,XY cell line remain unclear. Skin fibroblast culture and karyotyping would have been useful in this case, but unfortunately the patient has left Kuwait permanently.

Acknowledgment

We thank Professor J. P. Fryns for reviewing the manuscript.

References

1. Vergnaud G, Page DC, Simmler MC, et al. A deletion map of the human Y chromosome based on DNA hybridization. Am J Hum Genet 1986;38(2):109-24.
2. Davis RM. Localisation of male determining factors in man: a thorough review of structural anomalies of the Y chromosome. J Med Genet 1981;18(3):165-95.
3. Buhler EM. A synopsis of the human Y chromosome. Hum Genet 1980;55(2):145-75.
4. Fryns JP, Kleczkowska A, Lemmens P, Van Den Berghe H. Unusual in vivo rearrangements of the Y chromosome in two males. Clin Genet 1987;31(3):132-6.
5. Hiraishi Y, Iinuma K, Kato M, et al. Unusual karyotypic variability associated with a dicentric Y chromosome in an intersex girl. Clin Genet (in press).
6. Cohen MM, MacGillivray MH, Capraro VJ, et al. Human dicentric Y chromosomes: case report and review of the literature. J Med Genet 1973;10:74-9.
7. Giraud F, Mattei JF, Lucas C, et al. Four new cases of dicentric Y chromosomes. Hum Genet 1977;36(3):249-60.
8. Schmid W, D'Apuzzo V. Centromere inactivation in a case of Turner variant with two dicentric iso-long arm Y chromosomes. Hum Genet 1978;41(2):217-23.
9. Fryns JP, Cassiman JJ, Van Den Berghe H. Unusual in vivo rearrangements of the Y chromosome with mitotic instability in vitro. Hum Genet 1978;44(3):349-55.
10. Rosenfeld RG, Luzzatti L, Hintz RL, et al. Sexual and somatic determinants of the human Y chromosome: studies in a 46,XYp- phenotypic female. Am J Hum Genet 1979;31(4):458-68.
11. Fitch N, Richer C, Pinsky L, Kahn A. Deletion of the long arm of the Y chromosome and review of Y chromosome abnormalities. Am J Med Genet 1985;20(1):31-42.
12. Bostock CJ, Gosden JR, Mitchell AR. Localisation of a male-specific DNA fragment to a sub-region of the human Y chromosome. Nature 1978;272(5651):324-8.

Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, and letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

The Evolution of University-Based and Certified Postgraduate Medical Education

To the Editor: The progress achieved in postgraduate medical education in the Kingdom of Saudi Arabia has been aptly described as "remarkable," and the available postgraduate medical education programs have been reviewed.[1,2] Worldwide, medical curricula, those documents which are "many things to different people,"[3] are being reassessed. Although curriculum is axiomatic to the educational process, in postgraduate medical education, there is no agreement on some of its fundamental aspects.

For example, how much information should the curriculum contain? Should it be student- or teacher-centered? On which system should it be based, the annual or the credit hour? Should it be structured at all? If it is structured, to what extent? Indeed, by which institution in the first place should postgraduate medical education be provided? Should it be university-based? If it is, shouldn't the certifying body be independent of the university? And so on.

The purpose here is to trace the evolution of a postgraduate medical education set-up, with particular reference to the formulation of its programs and curricula. We have reason to believe that these may be of general interest in the way in which hitherto conflicting aspects of postgraduate medical education curriculum design and implementation have been successfully blended. Furthermore, having been tested and found useful, the system is being proposed for general discussion and, it is hoped, for eventual wider trial.

King Faisal University (KFU) was founded in 1975 (1305H) in Dammam, Eastern Province, Saudi Arabia. The charter class of its Colleges of Medicine and Medical Sciences (CMMS) graduated in August 1981. In that same year, postgraduate medical education programs were initiated leading to the award of the "The Fellowship of KFU" in the specialty concerned. Thus, KFU combines the role of the education institution with that of the certifying body.

University Council approved the credit hour system and the programs' format (Table 1).

TABLE 1. *Students' questions and the answer sources in CMMS curricula for postgraduate medical education.*

	Question	Answer source
1.	What is the name of this course?	Title
2.	How long does it take?	Duration
3.	What are the prerequisites?	Prerequisite(s)
4.	What does it offer me?	Aim
5.	Why do I have to take this course?	Rationale
6.	What do I get at the end?	Objectives
7.	What is the content?	Course content
8.	What am I to put into it?	Minimum requirements
9.	What competences are expected of me?	Competence
10.	How am I going to be instructed?	Methods of instruction
11.	How am I going to be evaluated?	Evaluation
12.	What about reading material?	Reference

Objectives are written broadly as general instructional objectives rather than specific observable behaviors. Departments itemized instructional activities they considered as *minimum*, so that students (i.e., residents) are left in no doubt as to, say, the minimum weekly hours of work required of them. Similarly, the minimum contact hours for each course are also known, and from these, the credit hour equivalence can be computed. This undertaking proved to be more difficult than it sounds, consuming several committee meetings and stirring many a lively debate in Faculty Board.

The curricula are competency-based, competence being stated broadly in clinical or laboratory setting according to the specialty; the minimum required critical technical skills are also itemized. Evaluation procedures are described, and remedies/penalities for failures prescribed. The components include continuous assessment, log book, multiple choice questions, essays, and clinicals or practicals.

Continuous assessment is considered especially important. First, it is a mandatory component in all evaluations. Second, in some courses, satisfactory performance in the continuous assessment is a prerequisite to sit for the formal end-of-course test. Third, in other courses, formal tests are dispensed with, and grades are assigned on the basis of the continuous assessment. A few specialties require an inquiry-based dissertation (thesis), or case write-ups/course work, or both, thus providing that "judicious mixture of approved clinical training and inquiry-based theses."[4] Each program concludes with the requirements for the final certifying examination, at which the participation of external examiner(s) is mandatory. Harden and associates[5] offered one model (SPICES) of curriculum planning in which he identified six educational strategies related to the curriculum. If the SPICES model is used, the profile for the KFU postgraduate programs becomes apparent. Thus, they are student-centered and problem-based, not integrated but discipline-based; they are community- and hospital-based as appropriate; they combine electives and standard program; and they are apprentice-based, being opportunistic rather than rigidly systematic. We hope that the KFU model here described provides an input for a future "Saudi Arabian Postgraduate Medical Board."[2]

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References

1. Herdson PB. The organization of postgraduate training in the Kingdom of Saudi Arabia. Ann Saudi Med 1987;7(1):1-2.
2. Al-Nozha MM, Taher S. Saudi Arabian Postgraduate Medical Board: will the dream come true? Ann Saudi Med 1987;7(3):175-6.
3. Walldren AW. Curriculum theory and curriculum practice: educational strategies for the health professions. WHO Public Health Papers 1974;61:9-17.
4. Parry KM. Medical education worldwide. Med Educ 1985;19:487-502.
5. Harden RM, Sowden S, Dunn WR. Some educational strategies in curriculum development: the SPICES model. Med Educ 1984;18:284-97.

The Need for a National Drug Formulary System in Saudi Arabia

To the Editor: The American Society of Hospital Pharmacists (ASHP) defines the formulary as "a continually revised compilation of pharmaceuticals (plus important ancillary information) that reflects the current clinical judgment of the medical staff." The ASHP also defines the formulary system as "a method whereby the medical staff of an institution, working through the pharmacy and therapeutic committee, evaluates, appraises, and selects from among the numerous available drug entities and drug products those that are considered most useful in patient care."

Once all currently used drugs are identified, referenced, documented, and cataloged, a well-designed formulary system performs a number of key functions and produces multiple benefits: It serves as an evaluative system for identifying and recommending discontinuing drugs in current use which give ineffective or suboptimal drug therapy. It reveals the use of drugs and combinations of drugs which have been authoritatively identified as products with questionable therapeutic value, safety, bioavailability, and cost effectiveness in clinical therapeutics.[1]

An efficiently designed formulary system is an essential element in effective inventory control and purchasing policies. When a formulary system acts as a drug identification and selection umpire, it paves the way for providing rational, high-quality generic product selection. This enhances the processes of competitive bidding and acquisition, which result in reducing inventories, their procurement costs, and carrying costs.[2,3] Formulary systems with stringent generic equivalency and single generic-equivalent purchasing policies have eliminated the procurement and carrying costs which normally occur when duplicate generic-equivalent drugs were purchased.[4-6]

The British National Formulary[7] publishes indications of relative costs of drug entities. This formulary includes cost-accounting codes for each drug entry and provides relative cost data for similar drug products not generically equivalent. This cost-accounting feature can be a first step to initiate the process of formulation, development, and implementation of a computerized drug utilization evaluation program. Drug utilization evaluation leads to cost-effective prescribing and rational drug therapy, and over the long term, the formulary becomes a mechanism to limit or eliminate the duplication of drug products in each therapeutic class.[8,9]

A well-designed fully automated formulary system can act as a mechanism to discourage over-prescribing and/or irrational prescribing by serving as an immediate data source of comparative information on drugs and serve as an excellent educational resource tool for enhancing doctors' drug knowledge. Consequently, physicians can make better decisions on whether, for example, a new product is a treatment of first or second choice, a last resort, or not worth consideration. Included in these decisions, an automated formulary system can be designed to assess a drug's real therapeutic gain (or lack thereof) to the patient. In addition, this formulary offers detailed practical guidance in using rational clinical pharmacology prescribing principles, noting explicitly where important drug data are lacking and estimating the frequency of adverse drug effects based on feedback from in-house incidence reports and published data analysis.[10,11]

As the complexity of drug therapy increases, formulary systems will need to address issues of substituting single-dose therapy for multiple-drug therapy, and oral or intramuscular therapy for intravenous therapy.[4] In addition, formulary systems can be designed to incorporate automatic stop-order and special order form policies for antibiotics and controlled substances requiring careful monitoring to prevent misuse. Special order forms for antibiotics in various studies decreased the duration of therapy and served as a mechanism by which to compile drug-use data concurrently.[11,12]

Arguments favoring implementation and utilization of a Saudi national drug formulary system are persuasive. Implementing a fully automated system holds great potential for fulfilling essential data-base management and information communication needs in drug distribution, drug information, and drug therapeutics throughout the Kingdom. Implementing such a system and using it well, however, will require the full attention, cooperation, and support of physicians, pharmacists, and allied health professionals throughout the Kingdom.

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References

1. The formulary system: brief history and 1960s perspective, excerpted from "Mirror to hospital pharmacy." Am J Hosp Pharm 1986;43:2838-9.
2. Rubin H, Keller DD. Improving a pharmaceutical purchasing and inventory control system. Am J Hosp Pharm 1983;40:67-70.
3. Swift RG, Ryan MR. Potential economic effects of a brand standardization policy in a 1000-bed hospital. Am J Hosp Pharm 1975;32:1242-50.
4. Abramowitz PW, Fletcher CV. Counterpoints: let's expand the formulary system and renew its vigor. Am J Hosp Pharm 1986;43:2834-8.
5. Rosner MM. The financial effects of formularies in hospitals. Am J Hosp Pharm 1966;23:673-5.
6. Green JA. Point: the formulary system and the emperor's new clothes. Am J Hosp Pharm 1966;43:2830-4.
7. British Medical Association and the Pharmaceutical Society of Great Britain. British National Formulary. London: Bath Press, 1986.
8. Senthilkumaran K, Shatz SM, Kalies RF. Computer-based system for formulary decisions. Am J Hosp Pharm 1987;44:1362-6.
9. Sateren LA, Sudds TW, Tyler LS. Computer-based system for maintaining and printing a hospital formulary. Am J Hosp Pharm 1987;44:1367-70.
10. Herxheimer A. Basic information that prescribers are not getting about drugs. Lancet 1987;1(8523):31-3.

11. Durbin WA Jr, Lapidas B, Goldmann DA. Improved antibiotic usage following introduction of a novel prescription system. JAMA 1981;246(16):1796-800.
12. Kowalsky SF, Echols RM, Peck F Jr. Preprinted order sheet to enhance antibiotic prescribing and surveillance. Am J Hosp Pharm 1982;39:1528-9.

Congenital Dislocation of the Hip

To The Editor: It is clear from the recent editorial by Hugh Watts, "The early detection of congenital dislocation of the hip,"[1] and the article by Al-Umran et al, "Neonatal screening for hip stability,"[2] that congenital dislocation of the hip (CDH) exists in Saudi Arabia. Even though we are unaware of the exact incidence, the situation does cause concern, more so when it has been observed by Mufti in his article, "Prime factors in the etiology of congenital dislocation of the hip and talipes equinovarus in Riyadh," that bilateral congenital dislocation of the hip is more common then unilateral dislocation in this region.[3]

The cause of the condition is still unknown, but there exists in Saudi Arabia a tradition termed *mehd* in Arabic, whereby neonates and infants are swaddled in clothing, and around this a bandage is applied. It is changed once or twice daily and maintained for the first few months of life. The mothers believe that this method of swathing, which maintains the lower limbs in forced extension, is conducive to the development of straight legs. It has been reported that in certain ethnic groups, such as the American Indians or the people of the Arab village of Hebron where infants are swaddled with legs extended, there is a higher incidence of CDH.[4]

The incidence of congenital hip abnormalities in Japan before 1965 was 5% to 6% and CDH ranged from 1.1% to 3.5%. This has now declined to 0.6% and 0.2%, respectively. The high incidence was attributed to the Japanese tradition of applying a swathing diaper which maintained the infant's legs in extension. This resembled the "cradle board" of the Navajo Indians, where again the incidence of CDH was 6%.[5] The reduced incidence in Japan is attributed to Ishida's efforts in improving child care and avoidance of prolonged extension of the hips and knees in early infancy.[6]

Animal experiments and clinical study of newborn infants have shown that the main mechanical factor causing hip dislocation is prolonged tension of the iliopsoas and hamstring muscles and that each of these muscles has a synergistic effect in the production of hip dislocation. In the perinatal period, the muscular balance of the fetus is in the flexor dominant position, and the femoral head of the infant lies deep within the acetabulum. In the breech position the hamstrings are stretched and their prolonged tension may cause distal displacement of the femoral head during the intrauterine period. In the neonatal period, when the hips and knees are forcibly extended, either by the diaper or baby clothing, the iliopsoas and hamstrings are under tension and may cause subluxation or dislocation of the hip. So Yamamuro and Ishida presumed that the main factors predisposing the dislocation of the hip are prolonged tension on the hamstrings in the perinatal period and prolonged tension on the hamstrings and iliopsoas in the postnatal period. Therefore, to prevent the postnatal development of the hip dislocation in newborn babies, prolonged extension of the hips and knees should be avoided.[5]

It may be presumed that in Saudi Arabia the incidence of congenital dislocation of the hip in general and that of bilateral CDH in particular may be high due to the use of *mehd*. It is obvious therefore that in addition to neonatal screening for hip instability, we should initiate a national campaign against the use of *mehd*.

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References

1. Watts H. The early detection of congenital dislocation of the hip. Ann Saudi Med 1988;8(6):423-4.
2. Al-Umran K, Ahlberg A, Dawodu AH, et al. Neonatal screening for hip instability: five years' experience. Ann Saudi Med 1988;8(6):425-9.
3. Mufti MH. Prime factors in the etiology of congenital dislocation of the hip and talipes equinovarus in Riyadh. Ann Saudi Med 1988;8(1):29-34.
4. Wilkinson JA. Prime factors in the etiology of congenital dislocation of the hip. J Bone Joint Surg Br 1963;45:268-83.
5. Yamamuro T, Ishida K. Recent advances in the prevention, early diagnosis, and treatment of congenital dislocation of the hip in Japan. Clin Orthop 1984;184:34-40.
6. Ishida K. Prevention of the development of the typical dislocation of the hip. Clin Orthop 1977;126:167-9.

Dr. Hussain's letter was referred to Dr. Watts, the author of the Editorial relating to "Congenital dislocation of the hip," who made the following comments:

The whole problem of baby swaddling has been a matter of concern for a long time. The Italians, who certainly used to swaddle their babies, had a very high incidence of congenital dislocation of the hip. Whether this was due to swaddling or to a genetic aspect is uncertain. Certainly, the Japanese experience is important.

Dr. Hussain's point is valid and the campaign he suggests to discourage *mehd* would be appropriate.

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The Coincidental Occurrence of Squamous Cell Carcinoma of the Tongue and Tuberculosis

To the Editor: Squamous cell carcinoma of the tongue may present with associated cervical metastases.[1] In this case the associated presence of cervical lymphadenopathy was in fact due to active tuberculosis.

A 35-year-old man was referred to the otolaryngology unit for investigation of a lesion on the right side of his tongue, which had been increasing in size over a 6-month period. The patient smoked 10 cigarettes per day but did not take alcohol. He was otherwise completely fit. He had lived and worked in the United Kingdom for 5 years, having previously lived in Bombay.

Physical examination showed a lesion on the right lateral border of the tongue in the anterior two thirds. It was approximately 0.5 cm in diameter, soft, and with no evidence of spread beyond its palpable margins. Examination of the neck revealed a soft, fluctuant, ipsilateral swelling in the midcervical region of the anterior triangle. The swelling was 1.5 cm in diameter and mobile. Neither of these lesions had a characteristically malignant appearance, and the patient's age and history were also felt to make malignancy unlikely.

The patient was admitted to the hospital and prepared for surgery. Results of preoperative investigations, which included a chest roentgenogram, hemoglobin estimation, and leukocyte count, were all normal. The tongue lesion was excised with adequate margins and submitted to frozen-section examination. The histologist reported the lesion to be suspicious of invasive squamous cell carcinoma. In view of this degree of uncertainty, it was decided to proceed no further until full histologic evaluation of the paraffin sections. A fine-needle aspiration was performed on the neck mass, but the specimen showed only epithelioid cells.

Paraffin sections were reported as demonstrating that invasive squamous cell carcinoma was present in the tongue biopsy specimen, but that it had been completely excised.

In view of these findings the patient was advised that the neck mass should be biopsied, and if this showed evidence of squamous cell carcinoma on frozen section, then a radical neck dissection would be carried out. The patient subsequently underwent excision biopsy of the neck node, and frozen section showed histologic features of tuberculosis with no evidence of malignancy. Subsequent full histologic and bacteriologic reports confirmed the presence of acid-fast bacilli and the diagnosis of tuberculosis.[2]

The patient made an uneventful recovery from the operative procedures and began a course of antituberculous chemotherapy which included rifampin, isoniazid, and pyrazinamide over a period of 6 months. The patient has shown no evidence of further malignant or tuberculous disease in 1 year of follow-up.

The synchronous occurrence of lingual carcinoma and tuberculous cervical adenitis is most unusual in the United Kingdom but would appear to be more common abroad.[3,4] It illustrates the importance of considering the possibility of such dual pathologies. The performance of an excision biopsy of the neck node provided important information which helped to avoid more extensive surgery. It is also important to remember that in the course of patient follow-up either disease may show evidence of recurrence and must be managed appropriately.

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References

1. Wright D, Kenyon G. Cancer of the neck. In: Kerr AG, ed. Scott Brown's otolaryngology, vol 15, 5th ed. London: Butterworth, 1987:315-39.
2. Stell PM, Maran AG, eds. Tuberculous cervical nodes. In: Head and neck surgery. Philadelphia: Lippincott, 1978:106-7.
3. Comoretto R. Association of cancer of the base of tongue and tuberculosis. Min Otorhinolaryngol 1968;18:50-7.
4. Weatherall DJ, et al, eds. Increased incidence of tuberculosis in Asians. In: Oxford textbook of medicine. Oxford, England: Oxford University Press, 1987:282.

Book Review

Pathology
E Rubin, JL Farber, eds.
J.B. Lippincott Company, 1988
Philadelphia, PA, USA
1824 pages, US $59.95

This magnificent, entirely new textbook of pathology is the work of 40 contributors, two of whom have edited the 29 chapters.

The book includes photographs of patients, gross specimens, histology and electron microscopy, together with clear, concise line drawings and striking diagrams. The beautiful illustrations are the work of Dimitri Karetnikov. There are more than 1750 color illustrations and black-and-white photomicrographs.

The text is clearly written, concise, and of a remarkably consistent style—a tribute to the obviously close collaboration between the editors, the contributors, and the artist. And the information is up-to-date and comprehensive. The first nine chapters cover modern general pathology, and the remaining 20 deal with systemic pathology.

The most important advance over other, older textbooks is that this tome not only provides excellent coverage of general and systemic pathology, but also integrates this information with contemporary biology and clinical medicine.

The editors are well known as first-rate diagnostic pathologists, with a wealth of background in experimental pathology and in teaching. And the list of 38 other contributors is representative of the very best of modern North American pathologists, working in some of the most prestigious departments in the United States and Canada.

To produce such a comprehensive, well-illustrated, up-to-date and well-written textbook of pathology for the stated price of US $59.95 is a remarkable achievement.

Pathology can be recommended as a first-rate textbook for undergraduate medical students, as well as for postgraduate trainees in all medical disciplines. And the work should be available in all pathology departments and hospital and medical school libraries.

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SYMPOSIUM ON NUTRITION

King Faisal Specialist Hospital and Research Centre, Riyadh
10-11 Jumada Al-Thani 1409 (17-18 January 1989)

Malnutrition remains a major health problem in the world today. Here in Saudi Arabia, we always hear malnutrition spoken of in terms of undernutrition and overnutrition. Many deaths among children are attributed to undernutrition while deaths among adults are caused by diseases related to obesity (overnutrition), such as diabetes, cardiovascular diseases, and hypertension.

Several factors give rise to the problem of malnutrition. The main factor is the lack of well-trained Saudi nationals in the field of food, nutrition, and dietetics to inform and educate the public on the important role of proper nutrition in the prevention and treatment of debilitating and fatal diseases.

From the lectures and discussions in the Symposium, it was concluded that there is a great need for proper nutrition education of the different sectors of society—government, health professionals, scholars, and laymen. Mass media should be used effectively for nutrition information dissemination and dietary guidance of the general public, both literate and illiterate populations. A sound national nutrition education program with the participation of mass media will surely lead to the improvement of health of our patients and the community of Saudi Arabia as a whole.

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Research Centre

NUTRITIONAL MANAGEMENT OF DIABETES, MJ Franz, International Diabetes Center, Minneapolis, Minnesota, USA

The goals of nutritional management of diabetes are (1) normalization of blood glucose and lipids; (2) attainment and maintenance of a reasonable body weight; and (3) provision of a nutritionally adequate diet. Recommendations for persons with diabetes are similar to many heart, cancer, and other health organization's nutritional recommendations. Nutritional recommendations and controversies relate to calories, percentage and type of carbohydrate (sucrose, fiber, glycemic index); role of protein in the development of renal disease; fat concerns (omega-3's, monounsaturated, cholesterol); nutritive and nonnutritive sweeteners; salt, vitamins, and mineral supplementation. Educational tools (exchange lists) have been revised to reflect current nutritional recommendations. The ultimate goal and approach to nutrition education and counseling is to target positive behavioral changes in patients with diabetes. Persons with NIDDM need to understand the relationship of obesity to diabetes, set realistic weight goals, understand the importance of spreading calories throughout the day, and how to incorporate exercise into their lifestyle. Persons with IDDM need to have an individualized meal plan and insulin integrated into their usual eating habits, goals prioritized, and phased education. Continuing education and counseling are essential if change is to continue.

TOTAL PARENTERAL NUTRITION (TPN) FOR CHILDREN WITH CANCER, RJA Aur, King Faisal Specialist Hospital and Research Centre, Riyadh

A large number of children with cancer require strong nutritional support prior to any form of therapy. In an effort to prevent the development or progression of cachexia, nutritional therapy must be used frequently as an adjunctive measure. To administer TPN solutions, it is necessary to cannulize the central venous circulation. These solutions are hyperosmolar and must be administered through a vessel with a high flow rate so as to decrease the risk of phlebitis and thrombus formation. Indications for removal of the catheter include catheter infection, accidental dislodgement, leakage or severing of the catheter, and when the catheter is no longer needed. The components of TPN solutions are hypertonic glucose, protein (casein hydrolysates or amino acid solutions), fat emulsions usually of soybean origin, electrolytes, vitamins, and trace elements. Glucose (dextrose) is used as 20% to 25% solution. The amount and rate should not exceed 1 g/kg/h. Protein requirements are usually 1.5 or 3.5 g/kg/d and are delivered as 2% to 3.5% solutions of amino acids. Lipids are usually given as a 10% fat emulsion, usually 1 to 4 g/kg, and this should not exceed 50% of the total caloric intake. The higher amount of lipids (4 g/kg/d) should only be given if there is no serious hepatic disease or hyperlipemia. Additional increases in caloric intake (12% to 100%) must be considered in cases of fever, sepsis, major surgery, and severe growth failure. Hyperalimentation of malnourished cancer patients may prevent death from starvation and may restart an adequate tolerance to chemotherapy. Malnourished children with cancer, for whom chemotherapy is planned, must receive parallel nutritional support.

AN OVERVIEW OF DIABETES MELLITUS IN THE KINGDOM OF SAUDI ARABIA, M Ahmed, King Faisal Specialist Hospital and Research Centre, Riyadh

The prevalence of diabetes mellitus in the Kingdom is 3% to 6%. It increases with increasing age (13% in subjects over 55 years) and improvement in socioeconomic status. Over 85% of patients have noninsulin-dependent diabetes mellitus (NIDDM). The distinctive clinical features of type II Saudi diabetic population are (1) obesity in 85% of patients (BMI 27 ± 5.2 kg/m^2) at presentation; (2) rarity of polyuria; and (3) normal blood pressure readings (87%). Associated biochemical features include moderately severe hyperglycemia; relative insulin deficiency; normal serum cholesterol; hypovolemia; and hyperosmolarity. Type II Saudi diabetic patients exhibit rarity of ketotic and nonketotic hyperglycemic coma and of microvascular and macrovascular complications. It is postulated that normal blood pressure and cholesterol values probably explain the lower incidence of vascular complications.

NUTRITIONAL ASSESSMENT OF SAUDI PATIENTS WITH MEDICAL RISK FACTORS, ZB Ali, M Luarca, Aramco Dhahran Health Center

This study was a nutritional status assessment of Saudi patients with medical risk factors as a percentage of total patients attending the Dhahran Health Center Outpatient Diet Clinic. Data of this study provided information on diet history, weight, related blood levels, and physical activities. A comparison was made of these factors prior to and after diet assessment and instruction touching on compliance of these patients. Data will be collected from individual care plans and follow-up visits for a minimum of 6 months.

INFANT-FEEDING PATTERN AND WEANING PRACTICES IN KUWAIT, EK Amine, F Al-Aawadi, M Rabie, High Institute of Public Health, Alexandria, Egypt

A survey was implemented to investigate infant-feeding and weaning practices in Kuwait. The study included 2994 mothers of children less than 3 years. The results showed that 60.6% of the infants were breast-fed, 13.6% were bottle-fed, and 25.8% received mixed feeding. The mean duration of breast-feeding was 5.8 months and varied from 9.5 to 4.3 months among illiterate and educated mothers, respectively. Older mothers were more likely to breast-feed their infants for a longer duration. On the contrary, mothers from high-income families were less likely to practice breast-feeding. The study revealed that 37.3% of the infants were weaned suddenly; the reasons for weaning were insufficient milk (30.3%), new pregnancy (14.5%), infant refusal (10.3%), mother's illness (11.9%), and reaching weaning age (12.1%). Foods used for weaning varied from infant formula (40.9%), homemade foods (17.4%), family food (5.7%), and a mixture of foods (16.3%).

A STUDY OF FACTORS AFFECTING THE PREVALENCE OF OBESITY AMONG ADULT FEMALES IN KUWAIT, F Al-Awadi, E Amine, Ministry of Health, Kuwait

Obesity is an important health problem in Kuwait. The aim of this study was to determine the prevalence of obesity among adult females. A multistage stratified sample of 2999 females was examined. The results revealed that the prevalence of obesity was 42.0%, while underweight was recorded among 2.4% of the sample. The prevalence of obesity was modified by several factors, as it was 46.8% among nonworking females and decreased to 34% among working women. Illiterate mothers were frequently obese (49.0%), and the prevalence decreased to 29% among females with university education. Husband's education had a similar effect, as the prevalence of obesity was highest (55.5%) among wives of illiterate husbands. The prevalence of obesity increased from 31.6% among mothers having one child to 59.4% among mothers having four or more children. Family income was inversely related to the prevalence of obesity which was 56.3% among females from low-income families and decreased to 35.3% among the high-income group. The age of adult females also contributed to the increasing prevalence of obesity among adult females.

OBESITY IN CHILDHOOD AND ADOLESCENCE, SV Ferguson, King Faisal Specialist Hospital and Research Centre, Riyadh

Obesity, defined as an excess accumulation of body fat, is a disorder with both familial and developmental contributions. Obese children generally have obese parents and siblings, but it is unclear whether environment or genetics is responsible. Psychological and social damage are probably the greatest problems of the obese child and adolescent. Weight control could be effective with proper guidance, but since adolescents are more vulnerable to unusual dietary practices which might interfere with increased nutritional needs, weight control should be delayed or modified until after the growth spurt. Behavior modification seems to be a more reliable and direct treatment for the obese. Changes can occur more rapidly than the tedious process of weight loss. If changes in behavior occur, then weight loss follows.

HEIGHT AND WEIGHT OF SAUDI PRESCHOOL CHILDREN, AR Al-Frayh, SS Wong, A Abanami, A Al-Omair, KN Haque, KR Adam, AM Barry, King Saud University, Riyadh

In Saudi Arabia, the growth standards frequently used for preschool and school-age children are those of Tanner, which are based on a survey in England in 1966. Accordingly, there has been a need for Saudi standards based on a representative regional sample. This paper presented the first growth standards for height and weight for Saudi preschoolers which have been developed based on a large cross-sectional sample of 6623 Saudi infants and children.

VEGETABLE PROTEINS IN PLANNING FOR CHILD NUTRITION, OM Galal, Nutrition Institute, Cairo, Egypt

Child nutrition problems in developing countries, including chronic undernutrition, iron-deficiency anemia, and vitamin A deficiency, can be counteracted at least in part by effectively targeted supplemental foods of appropriate composition. By developing such foods from locally available cereal and legume bases, the need for special child-targeted foods can be met in an economically sustainable manner. Local agricultural and other industries can be supported. The further advantage to this approach is that such products are likely to be used as supplements rather than replacements for breast milk. Milk-based formulas and other products which replace breast-feeding endanger the health of children and mothers under the circumstances obtaining in most of the developing world. Vegetable-based products, however, need not have these adverse effects, as they can be designed to complement rather than replace traditional patterns of infant-feeding.

TRAINING DIETITIANS AND OTHER RELATED FOOD SERVICE PROFESSIONALS IN THE KINGDOM OF SAUDI ARABIA, E Jaali, King Faisal Specialist Hospital and Research Centre, Riyadh

King Saud University is the major provider of the curriculum for training dietitians and other food service professionals in the Kingdom. Under the College of Applied Medical Sciences in the Department of Community Health Sciences, students study to become dietitians and nutritionists. The present program has been designed to teach students to become dietetic practitioners dealing professionally with nutritional problems in the Kingdom, in hospitals and community settings. King Faisal Specialist Hospital and Research Centre, Riyadh Al-Kharj Armed Forces Hospital, and King Khalid University Hospital collaborate with King Saud University to provide a 12-month internship for hospital dietitians. During these 12 months, students are trained using the guidelines of the ADA and BDA for developing and providing a hospital internship program for clinical dietitians, providing them with on-the-job training and experience in the field of dietetics under the guidance of professionally qualified and experienced clinical dietitians. Under the College of Agriculture in the Department of Agricultural Economics and Rural Sociology, women students study nutrition and home economics, 71 credit hours of study suited to Islamic social heritage and religious belief. Specific studies are designed to teach students to professionally help others to improve the everyday life in the community relating to social phenomena, hygiene, sanitation, food selection and preparation, child care and psychology, and in social research. Under this department, men study food science, 81 credit hours of courses.

PHENYLKETONURIA: NEONATAL SCREENING, DIAGNOSIS, AND NUTRITIONAL MANAGEMENT, CJ Olavo, Aramco Dhahran Health Center

Phenylketonuria and hyperphenylalaninemia designate a group of inborn errors of metabolism of phenylalanine. The defect may be caused by the absence or deficiency of phenylalanine hydroxylase or dihydropteridine reductase or lack of one of the sequential enzymatic steps in the synthesis of cofactor biopterin. Classic phenylketonuria has been linked to the absence or deficiency of phenylalanine hydroxylase and causes intellectual impairment if early detection and nutritional management are not initiated. It is one of the few disorders which justifies routine screening of neonates on a national scale. Sensitive and reliable methods of screening have been developed (an improvement on the use of ferric chloride) and applied to the entire newborn population in most developed countries. It has been found that the high cost of routine screening and early treatment is less than the cost of the long-term residential care required by most untreated cases. A routine screening program for phenylketonuria has been ongoing in Aramco for the last 5 years, and three patients with phenylketonuria have been detected. This review described the screening program, the early diagnosis, and the dietary management of these patients. Different low phenylalanine diet supplements used in phenylketonuria were also compared.

FOOD HABITS AND BELIEFS WITH REGIONAL CHARACTERISTICS IN THE KINGDOM OF SAUDI ARABIA, AK Osman, King Saud University, Riyadh

To be acquainted with and understand the food habits and beliefs of a population is the most important step in making nutrition education and counseling effective. The Kingdom is a large country with different geographical characteristics, it is a place where millions of pilgrims come every year to visit the holy places in Makkah and Medina, and through the centuries many of them have settled in the Kingdom. Due to that, many foodstuffs have appeared and become assimilated with the local diet which was once mainly whole wheat, dates, and milk. This paper described some diverse food habits and practices.

OVERVIEW OF NUTRITION IN THE KINGDOM OF SAUDI ARABIA, AI Al-Othaimeen, King Faisal Specialist Hospital and Research Centre, Riyadh

Studies in anthropometry and nutritional deficiency diseases and combined anthropometry and dietary survey studies have been conducted in the Kingdom. Anthropometric studies, mostly on preschool children in different regions, show mild to severe forms of malnutrition. Standards for weight for age, weight for height, and height for age by different investigators were used. Classifications of mild, moderate, and severe malnutrition by Gomez, Waterlow, and Waterlow and Rutishauser were applied. Anthropometric studies combined with dietary surveys showed mild and moderate degrees of malnutrition, usually in relation to height for age. This shows that Saudi infants and preschool children have normal weights but shorter stature than their Western counterparts. The most common deficiency diseases noted were anemia and rickets. Anemia is prevalent because of lack of dietary iron rather than microorganism infestation. Rickets is common because of lack of vitamin D which could be obtained from sunshine. Efforts by the government to improve the nutritional status of Saudi Arabians are now underway. A national nutrition survey to determine nutritional status of the people has reached its third phase of data gathering.

MEDICAL MANAGEMENT OF INBORN ERRORS OF METABOLISM, P Ozand, G Gascon, King Faisal Specialist Hospital and Research Centre, Riyadh

Maple syrup urine disease (MSUD) is an inherited disorder of metabolism resulting in the incapacity of the patient to metabolize the branched chain amino acids, leucine, isoleucine, and valine. The aim of successful management of MSUD is to reduce the blood level of leucine, which is neurotoxic. Two other disorders are known to occur with frequency in the Kingdom. These are 3-hydroxy-3-methylglutaryl coalyase (HMG coalyase) deficiency and isovaleric acidemia. These children must be given L-carnitine and an alkalinizing agent such as bicarbonate or Polycitra orally to prevent life-threatening acidosis and hypoglycemia. Unusual syndromes of hyperphenylalaninemia are present in the central region of the Kingdom; these syndromes present insidiously, not at birth, and are difficult to diagnose and manage clinically. This type of "malignant HPA" involves a defect in the synthesis of tetrahydrobiopterin (BH4), a common cofactor on many neurotransmitter synthesizing enzymes and phenylalanine hydroxylase. In addition to optimizing the phenylalanine intake, as monitored by frequent determination of blood phenylalanine, the patients must be given daily supplements of the lacking cofactor BH4. The drug management of the disease consists of the administration of L-5-hydroxytryptophane and 3,4-dihydroxyphenylalanine in conjunction with carbidopa and BH4. This is particularly important since, while early detection and management permit a normal lifestyle, late diagnosis or lack of awareness leads to death. Three other disorders found here in the Kingdom are methylmalonic acidemia, propionic acidemia, and multiple carboxylase deficiency. They require intensive medical management including peritoneal dialysis and biweekly aminograms, along with megadoses of biotin, vitamin B_{12} (hydroxocobalamine), and L-carnitine, and an alkalinizing agent to alleviate acidosis and prevent sudden death. Late detection causes irreversible brain damage, while early diagnosis prevents certain neurologic damage or death. Two types of glycogen storage disease were discussed: type I deficiency of glucose-6-phosphatase and type III deficiency of amylo-1,6-glucosidase. The crippling hepatomegaly is due to mobilization of fat from the adipose tissue and storage in the liver. The patient must be monitored frequently for hyperlipemia type I, hyperlactacidemia, hypercholesterolemia, and hyperuricemia.

DIET OF UROLITHIASIS PATIENTS IN THE KINGDOM OF SAUDI ARABIA,

WG Robertson, H Hughes, G Holbrow, S Louis, M Manawar, M Nisa, King Faisal Specialist Hospital and Research Centre, and I Husain, S Al-Faqih, A Chakrabarty, King Khalid University Hospital, Riyadh

A dietary survey carried out in 30 male middle-class Saudi stone-formers showed that they consumed higher amounts of animal protein and purine compared with the same group of stone-formers in the West. This was accounted for by the high consumption of lamb and chicken among the Saudis. More importantly, the Saudi patients also consumed about three times as much oxalate as Western stone-formers. This resulted from the consumption of certain high-oxalate-containing vegetables and tea without milk. Calcium intake was generally lower than in the West. The high acid-ash diet, combined with the high oxalate intake and lower calcium intake, accounted for the abnormal urine biochemistry and the relatively high risk of uric acid and calcium oxalate stones among Saudis.

MANAGEMENT OF HYPERCHOLESTEROLEMIA,

J Saour, King Faisal Specialist Hospital and Research Centre, Riyadh

This paper reviewed the evidence for the "lipid theory of atherosclerosis" and the most recent recommendations for management. Several animal studies have established that atherosclerosis can be induced in animals by increasing saturated fat and cholesterol intake. Epidemological studies have shown a relationship between hypercholesterolemia, high LDL levels, and incidence of CHD. An aggregate analysis of the 18 clinical trials published has shown that a reduction in serum cholesterol significantly reduces CHD. Small studies using repeated angiograms have shown that some atheromatous lesions were reversible with cholesterol-lowering treatment. Recently two international panels of experts addressed the management of hypercholesterolemia and came up with basically similar recommendations. Both panels agreed that along with smoking, obesity, and hypertension, hypercholesterolemia should be tackled in society as a whole as well as in individual patients. Individuals with total cholesterol of 6.20 mmol/L or with cholesterol level of 5.20 to 6.20 mmol/L plus two risk factors should be treated. Diet low in calories, saturated fat, and cholesterol and high in soluble fiber is the cornerstone of management. Failure of dietary therapy in 6 months should be followed by drug therapy.

TOTAL PARENTERAL NUTRITION USE IN ALL AND AML CHILDREN AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE,

V Rak, RA Frank, King Faisal Specialist Hospital and Research Centre, Riyadh

The goal of total parenteral nutrition during the stressful period associated with chemotherapy treatment in children with ALL and AML is to provide adequate nutrition allowing for continued physical development. A retrospective 12-month data collection during the year 1408H showed varying courses of TPN administration, percentages of nutritional needs met according to standard caloric and protein recommendations, and complications involving carbohydrate, fat, and protein intolerance. Electrolyte complications resulting from tumor lysis syndrome, although infrequent, are accounted for in the TPN formulation. Fluid limitations and large volumes of other intravenous infusions (blood products and antibiotics) often necessitate concentrating TPN solutions which may compromise nutritional goals. Children who present with complications such as long-term growth failure or sepsis require additional nutrient intake. These factors, coupled with an intolerance to any component of TPN, limit optimal intake, and the result of nutritional support in these patients is often limiting further malnutrition.

DIET THERAPY IN WEIGHT REDUCING IN BUKAYRIYAH, AL-QASSIM,

AK Al-Rayes, Al-Bukayriyah General Hospital, Al-Qassim

Weight reduction is especially important for individuals who suffer from a disease in which reduction of body weight is essential for their health. A survey was performed on 50 patients who attended the dietary clinic. The study revealed that the main reason for overweight in the citizens of Bukayriyah is their eating habits. Their carbohydrate intake is extremely high through eating food such as rice, garish, corsan, mataziz, and fats, especially the fat compound in meats. Most patients are referred to us from the diabetic clinic. Sixty percent of the diabetic patients surveyed had been advised by their doctors to lose weight, being told that by doing so they would become healthy and would not require medication to control their diabetic disease. Of those surveyed, 24% were advised to lose weight for other reasons, such as breathlessness on exertion, pain in the backbone, and the need for an operation. Eight percent suffered from hypertension and were advised to lose weight and also to reduce salt in food as much as possible. Four percent had heart disease, and 4% had atherosclerosis and were advised to reduce weight as well as reduce the cholesterol in their diet, e.g., animal fats, milk, liver, kidney, and especially egg yolk. It was noted that, of those surveyed, 60% were educated and 40% were uneducated. Of the educated people, 80% reduced their weight, 15% did not follow the advice to lose weight and remained the same weight, and 5% increased their body weight. The uneducated people differed from the educated people in that only 25% followed advice and reduced their weight, with 75% remaining overweight.

OPTIMAL NUTRITION FOR EXERCISE AND SPORT, AMA Shaker, Sports Medicine Hospital, Riyadh

Now more people than ever before are involved in exercise-related activities. Optimal nutrition is a basic training component necessary for the development and maintenance of top physical performance. All of the materials we have confirmed the important role of carbohydrate in exercise and the role of muscle glycogen as a chief source of energy. If an individual is physically active, the "prudent" diet should contain at least 50% to 60% of its calories in the form of carbohydrate starches. Some studies have shown that a high-fat diet enhanced endurance. It has also been suggested to avoid fat intake above 35% because of its association with atherosclerotic heart disease. Studies confirmed that high protein intakes have not been shown to be uniquely beneficial to athletes, and these studies recommended protein amount in the diet as 12% to 15%. All the studies have shown that deficiency of vitamins impairs physical performance. On the other hand, no evidence is available that vitamin intake above normally recommended quantities enhances physical performance. All the studies confirmed the importance of replacement of water and electrolytes during exercise. A well-balanced diet is the best choice for athletes. Additional food can be consumed to meet the energy needs, depending on the daily level of physical activity.

DIETARY MANAGEMENT OF INBORN ERRORS OF METABOLISM, E Thomas, King Faisal Specialist Hospital and Research Centre, and S Al-Orf, King Saud University, Riyadh

Dietary case histories of five KFSH patients affected by diseases involving inborn errors of metabolism were presented. The cases represented our experience with the dietary management of five different inborn errors of metabolism: (1) maple syrup urine disease, an inherited disorder of metabolism resulting in the inability of the patient to adequately metabolize leucine, isoleucine, and valine; (2) 3-hydroxy-3-methylglutaryl coalyase deficiency, another inherited disorder of metabolism which involves controlled amounts of the essential amino acid leucine; (3) methylmalonic acidemia, an inherited disorder involving the metabolism of four essential amino acids, methionine, threonine, valine, and isoleucine; (4) malignant hyperphenylalaninemia, an hereditary syndrome involving the metabolism of phenylalanine; and (5) glycogen storage disease, an inherited disorder affecting the metabolism of the simple sugars fructose and galactose. All of the presented disorders involve specific dietary management to permit a normal lifestyle. Uncontrolled diets lead to irreversible brain damage, abnormal growth pattern, and death.

FEEDING AND WEANING PRACTICES OF SAUDI PRESCHOOLERS, B Villanueva, King Faisal Specialist Hospital and Research Centre, Riyadh

Two nutrition surveys, one involving 767 preschool children between birth and 9 years of age and another composed of 849 Saudi children from birth to 6 years, were conducted to determine breast-feeding and weaning practices and at the same time gather information on anthropometric measurements and dietary intake. It was found that breast-feeding is still prevalent and widespread. Infants were breast-fed up to 2 years of age. Most of the mothers weaned at 6 months of baby's age. Age of the mother, education, and socioeconomic status affected their decision to wean their children. Weaning foods were introduced at 5.7 to 6 months of age. Anthropometric data revealed that Saudi children have heights for age lower than the NCHS standards, indicating mild to moderate malnutrition. One of the studies showed a mild degree of malnutrition when weight for height was measured. Data on dietary intake revealed that most of the nutrients were present in the Saudi children's diet except calories, iron, and niacin. This trend was pronounced when the children reached 1 year of age when the mother's milk failed to provide enough for the growing needs of the children, and a consequent failure to provide supplementary foods at the right time and in adequate amounts.

Announcements

The *Annals of Saudi of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least 6 months before the date of occurrence. Please send relevant information to the *Annals of Saudi Medicine*, Publications Office, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

18th International Epilepsy Congress

The 18th International Epilepsy Congress is scheduled for 18-22 October 1989 in New Delhi, India. The scientific program will include presentations on primary health care and epilepsy, epilepsy and surgery, prognosis in epilepsy, and new developments in antiepileptic drug treatment. Special sessions will include a patient forum, an evaluation of the classification of epilepsies and epileptic syndromes, and discussion of epilepsy, genetics, pregnancy, and the child. For additional information, contact Professor M. C. Maheshwari, Secretary General (18th IEC 1989), Department of Neurology, Neuro-Sciences Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India.

King Faisal Specialist Hospital and Research Centre Postgraduate Training Programs

King Faisal Specialist Hospital and Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, obstetrics/gynecology, pediatrics, and surgery.
2. Five-year pathology residency training program, affiliated with the Royal College of Pathologists of Australasia and the King Saud University.
3. Fellowships in cardiology (adult and pediatric), endocrinology, gastroenterology, infectious diseases, nephrology, and oncology (adult and pediatric).

For further information contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

King Saud University Hospitals Postgraduate Training Programs

King Saud University Hospitals (King Khalid University Hospital/King Abdul Aziz University Hospital) are pleased to invite applications for the following postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, pediatrics, surgery, and obstetrics/gynecology.
2. Diploma courses in medical radiodiagnosis, laryngology/otology, psychiatry, and family practice.
3. Master's degree courses in pathology and family practice.
4. Residency training program in ophthalmology (in conjunction with King Khaled Eye Specialist Hospital).

For further information, contact the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P. O. Box 2925, Riyadh 11461, Saudi Arabia.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

1. Doctors who hold MB,BS from King Saud University or equivalent degree with at least Good grade.
2. Doctors who have finished their internship in a recognized hospital with at least a Very Good grade.
3. Successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the whole period of training.

Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

Radiopharmaceuticals from King Faisal Specialist Hospital and Research Centre

King Faisal Specialist Hospital and Research Centre produces various radiopharmaceuticals at its Radionuclide and Cyclotron Operations facility with the aid of model CS-30 Cyclotron. These radiopharmaceuticals are produced according to international standards of good manufacturing practice. The Research Centre meets all the international standards of quality assurance and environmental safety with regard to radiopharmaceuticals.

Radiopharmaceuticals currently produced and available for distribution throughout the Kingdom and to adjoining Arab states are as follows: thallous (Tl-201) chloride injection ($T^{1}/2$ = 73 h); gallium (Ga-67) citrate injection ($T^{1}/2$ = 78.3 h); iodine-123 capsules ($T^{1}/2$ = 13.1 h); iodine-123 oral solution ($T^{1}/2$ = 13.1 h); iodine-123 orthoiodohippurate solution ($T^{1}/2$ = 13.1 h); rubidium (Rb-81) → krypton (Kr-81 m) generator ($T^{1}/2$ = 4.58 h → 13 s); indium (In-111) chloride injection ($T^{1}/2$ = 2.83 d); and iodine-124 solution ($T^{1}/2$ = 4.17 d).

Currently under development are indium (In-111) oxine for cell labeling; indium (In-111) DTPA for cisternography; I-123-labeled mIBG for imaging adrenergic tumors; and I-123-labeled fatty acids for evaluation of myocardial fatty acid metabolism. Suggestions from the medical community for additional radiopharmaceuticals are welcome.

Inquiries concerning the availability, price schedule, and technical information on specific radiopharmaceuticals should be directed to Abbass H. Al-Marzouky, MD, Executive Director, Research Centre, King Faisal Specialist Hospital and

Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 2900; telex 401050 ROSPEC SJ; telefax 464-7272, extension 1049.

Second International Conference on Systemic Lupus Erythematosus

The National Arthritis Foundation of Singapore and the Society of Immunology and Rheumatology are organizing the Second International Conference on Systemic Lupus Erythematosus to be held 26-30 September 1989 in Singapore. The meeting will combine clinical and scientific plenary sessions, seminars, and free papers. For further details, contact Dr. P. H. Feng, Chairman, Organizing Committee, Second International Conference on SLE, Department of Medicine IV, Tan Tock Seng Hospital, Moulmein Road, Singapore 1130; telephone (65)-3508214; telex RS 39675 TTSH.

Riyadh Armed Forces Hospital Symposia

The Armed Forces Hospital of Riyadh has announced the following calendar of upcoming symposia:

1. International Symposium on Advanced Medicine II, 17-19 September 1989.
2. Advances in Neurology and Neurosurgery, 1-2 October 1989.
3. Medical and Surgical Aspects of Hepatobiliary Disease, 19-20 November 1989.
4. Symposium on Atherosclerosis, 26-27 November 1989.
5. Modern Trends in the Management of Valvular Heart Diseases, 14-17 January 1990.

For additional information, contact the Department of Medical Studies, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia; telephone (01) 477-7714, extensions 2269, 3548, 3549, 3550; telex 401645 RKHPA SJ; telefax 477-9168.

King Faisal Specialist Hospital and Research Centre Symposia for 1410

King Faisal Specialist Hospital and Research Centre has scheduled the following postgraduate education symposia:

1. Health Care Manpower Symposium, 3-4 October 1989 (4-5 Rabi Al-Awal 1410).
2. Fourth Annual Radiology Symposium, 10-11 October 1989 (11-12 Rabi Al-Awal 1410).
3. Symposium on Preventive and Restorative Dentistry, 17-18 October 1989 (18-19 Rabi Al-Awal 1410).
4. Annual Pathology Symposium, 31 October-1 November 1989 (2-3 Rabi Al-Thani 1410).
5. Pharmacy Practice in Saudi Arabia: Current and Future Trends, 13-15 November 1989 (15-17 Rabi Al-Thani 1410).
6. Annual Neonatology Symposium, 28-29 November 1989 (30 Rabi Al-Thani-1 Jumada Al-Awal 1410).
7. Fine-Needle Biopsy Tutorial, 5-7 December 1989 (7-9 Jumada Al-Awal 1410).
8. Symposium on Malignancies in Childhood, 6-7 February 1990 (11-12 Rajab 1410).
9. Third Annual Symposium on Excellence in Nursing, 26-28 February 1990 (1-3 Shaban 1410).
10. Symposium on Nonsurgical Management of Low Back Pain, 10-11 March 1990 (13-14 Shaban 1410).

For additional information, please contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

IX Biennial International Congress of Cardiology

The Pakistan Cardiac Society has announced the IX Biennial International Congress of Cardiology to be held in Lahore, Pakistan, 7-10 December 1989. The official language of the program is English. For additional information, contact the Organizing Secretary, Congress Secretariat, Department of Cardiology, Mayo Hospital, Lahore, Pakistan; telephone (042) 310130, extension 13; telex 44516 HINON PK; telefax 92-42-871715.

Second Annual International Course on Magnetic Resonance Imaging

The Departments of Radiology and Medical Studies of the Riyadh Armed Forces Hospital will sponsor a course on magnetic resonance imaging on 2-5 October 1989 (3-6 Rabi Al-Awal 1410) in the main lecture theater of the Hospital. The course will provide a comprehensive overview of MRI technology and up-to-date methodology, present and future uses of MRI in the whole body, small group workshops, and access to the MRI teaching file.

The fee is SR1000 for physicians and SR500 for medical staff in training.

For additional information, contact the Department of Medical Studies, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia; telephone (01)477-7714; telefax 477-9168.

Annual Pathology Symposium

This year the Annual Pathology Symposium at King Faisal Specialist Hospital and Research Centre will concentrate on the pathogenesis of infections in the immunocompromised host. The program will be held on 31 October and 1 November 1989 (2-3 Rabi Al-Thani 1410).

Topics will include the following: the making of a compromised host; endocrine dysfunction and microbial disease; infection in blood transfusion recipients and drug abusers; neoplastic disease and microbial infections; histopathology of infected lung in the compromised host; histopathology of infected brain in the compromised host; infections in bone marrow transplant recipients; yeast infections, bacterial and nontuberculous mycobacterial infections in compromised patients; chlamydial and viral infections in compromised hosts; monoclonal antibodies in the laboratory diagnosis of infections; antibodies and microbial pathogenesis in the compromised host; and patient management and antimicrobial therapy. In addition, there will be sessions devoted to postgraduate training in pathology in the Kingdom.

For further information contact the Director, Academic Affairs and Postgraduate Medical Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

International Conference on Emergency Health Care Development

An International Conference on Emergency Health Care Development will be held in Washington, DC, 15-18 August 1989. The conference is being organized by Medical Care Development International in collaboration with the US Public Health Service, the Pan American Health Organization, the Federal Emergency Management Agency, the United Nations Disaster Relief Office, and other national and international organizations that deal with emergency health care issues.

The conference will focus on issues related to the development and upgrading of emergency health care services on a worldwide basis. The goal is to achieve a consensus on a world concept of emergency health care that is not limited to Western-oriented, technologically defined emergency medical services. It will examine methods of building and improving the ability of health care systems to respond to routine medical emergencies and to coordinate the additional resources needed for response to mass casualty incidents and disasters. The conference will address the organization of emergency health care in urban and rural areas of industrialized and developing countries. Representatives of international funding organizations will review potential methods of funding emergency health care system improvements. The faculty will include emergency health care specialists from outside the United States, and participants are expected to include representatives from many countries of the world.

The conference is open to all emergency health care professionals and planners/managers of health care services.

Information regarding the conference program or registration can be obtained from EHC Conference, MCD International, 1742 R St., NW, Washington, DC 20009, USA; telephone (202) 462-1920.

First Mediterranean Symposium on Immunometric Assays

This symposium, which is sponsored by the Faculty of Medicine, Naples, Italy, will take place on September 20-22, 1989, in Naples, Italy. The meeting will gather experts from around the world, particularly from the Mediterranean countries, and will consider aspects of immunometric assays, including infectivity, tumor markers, and sterility/fertility. Further information may be obtained from the Organizing Secretariat, CLAS International, Via Pace, 8-25122, Brescia, Italy. Phone 030/48006-59454; telefax 030/293282; telex 300070 CLAS I.

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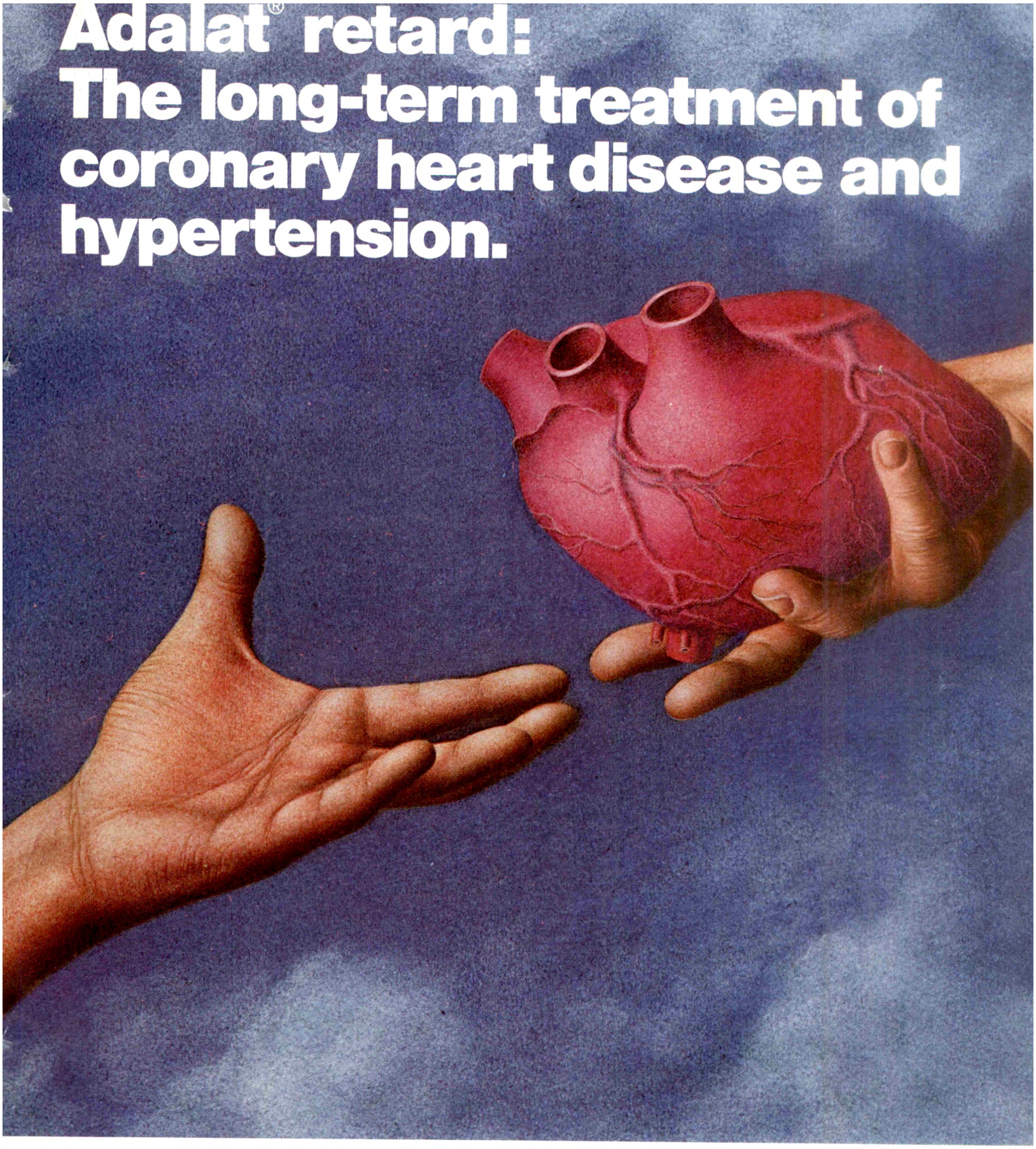

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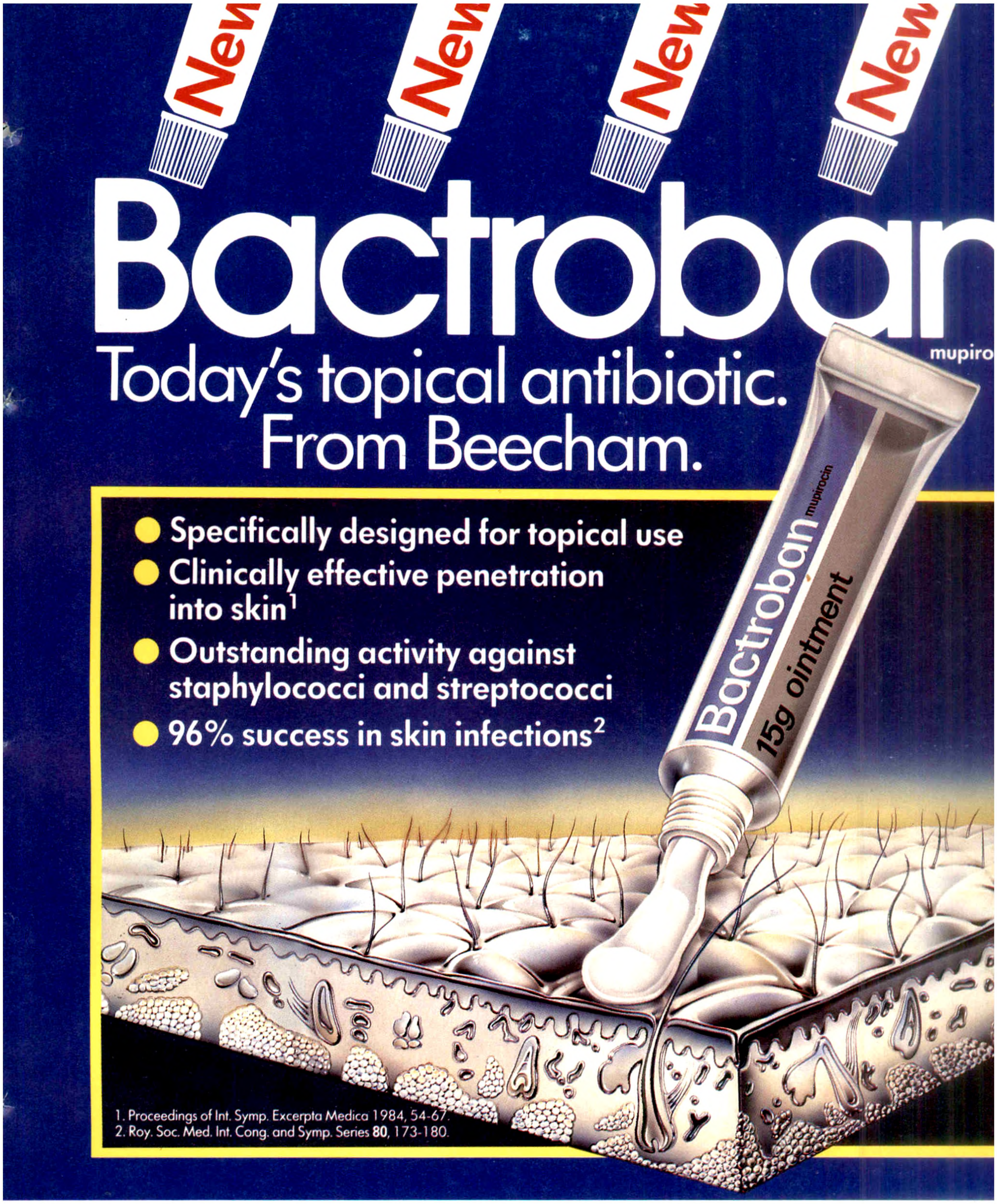

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Aims and Scope

The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is typeset and printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal*, established in 1980.

The *Annals* is a bimonthly multidisciplinary medical journal. High-quality papers, written in English, dealing with aspects of clinical, academic or investigative medicine or research will be welcome. Emphasis is placed on matters relating to medicine in Saudi Arabia in particular, and the Middle East in general, though articles are welcome from anywhere in the world, and the *Annals* has worldwide readership.

The *Annals* publishes original articles, case reports, letters to the editor, editorials, and from time to time, special communications, commentaries, and review articles. Abstracts of meetings and symposia sponsored by the Joint Board for Postgraduate Medical Education of Saudi Arabia are published, and the proceedings of such symposia may be published if the Editorial Board considers them appropriate and relevant. The Editorial Board wishes to minimize delay between manuscript submission, decision, and publication, and accordingly authors are requested to follow carefully the instructions set out under "Information for Authors."

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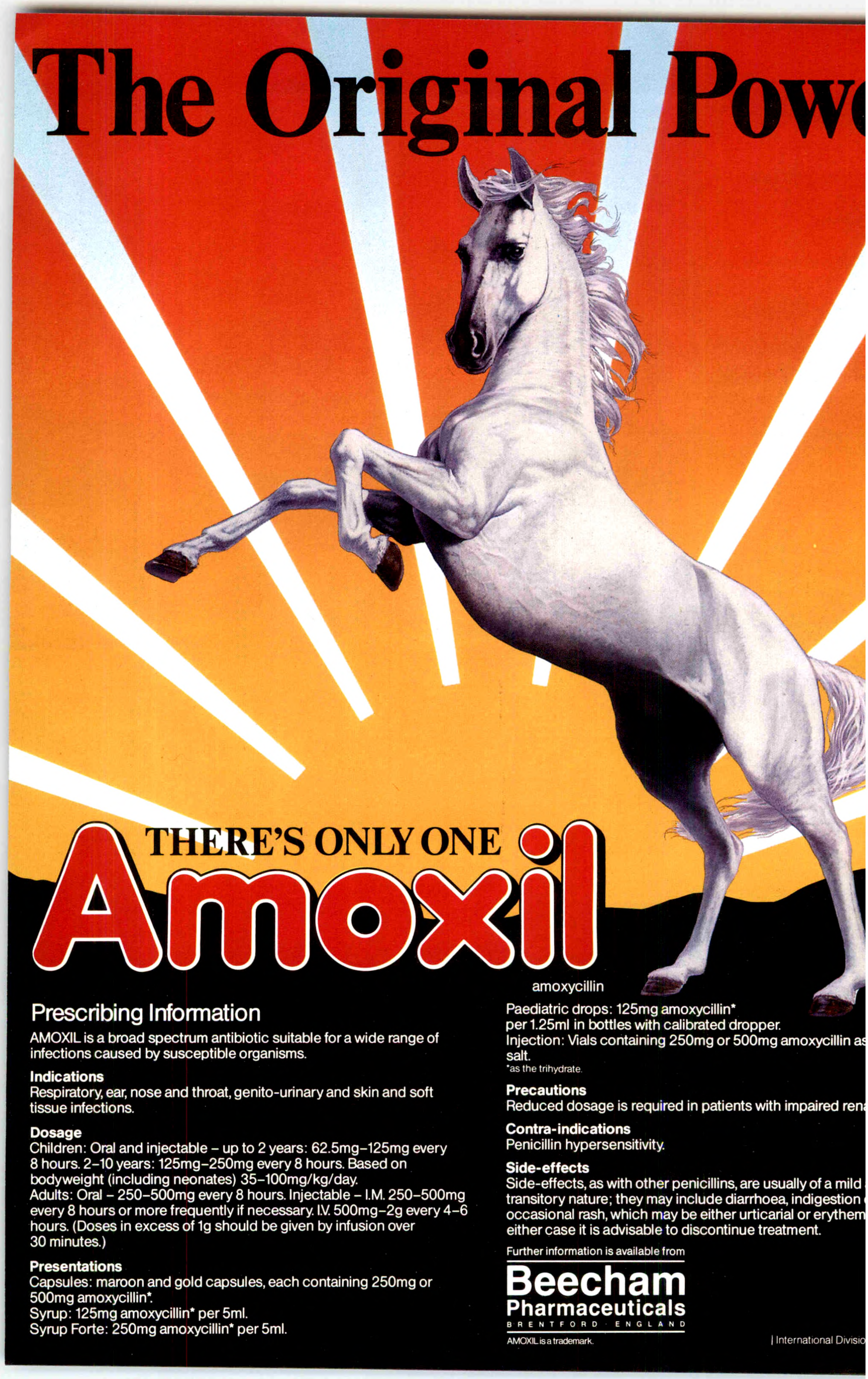

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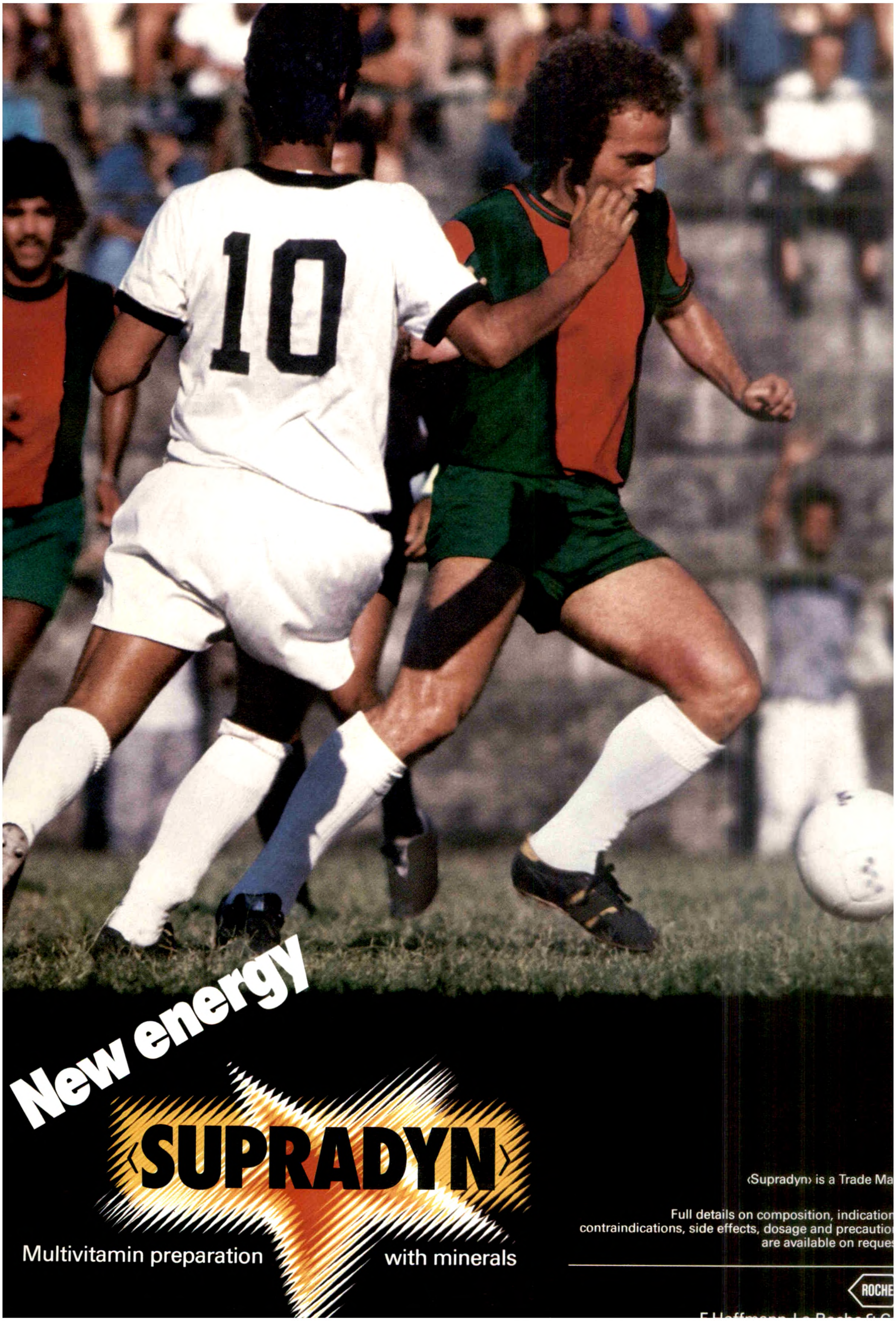

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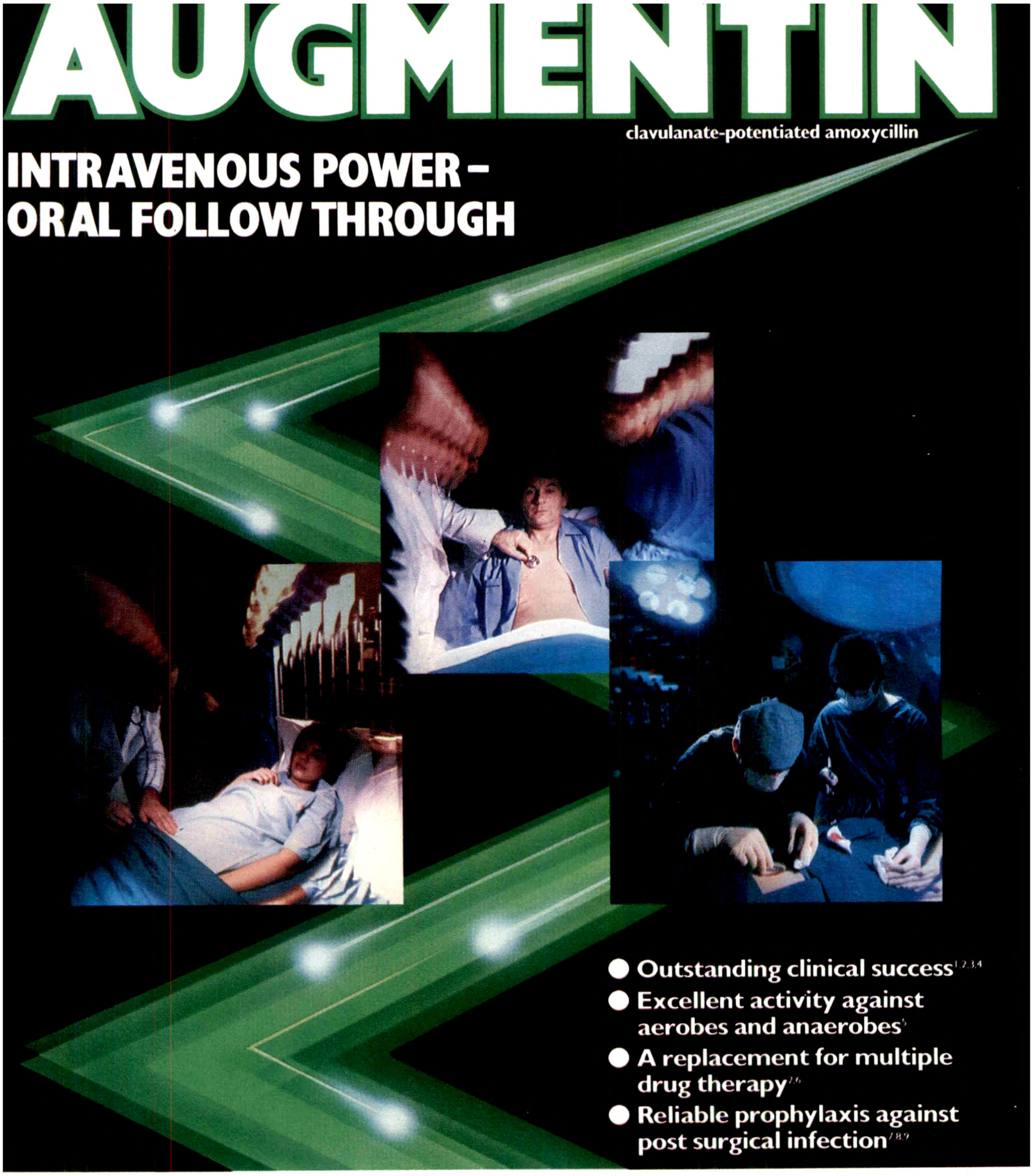
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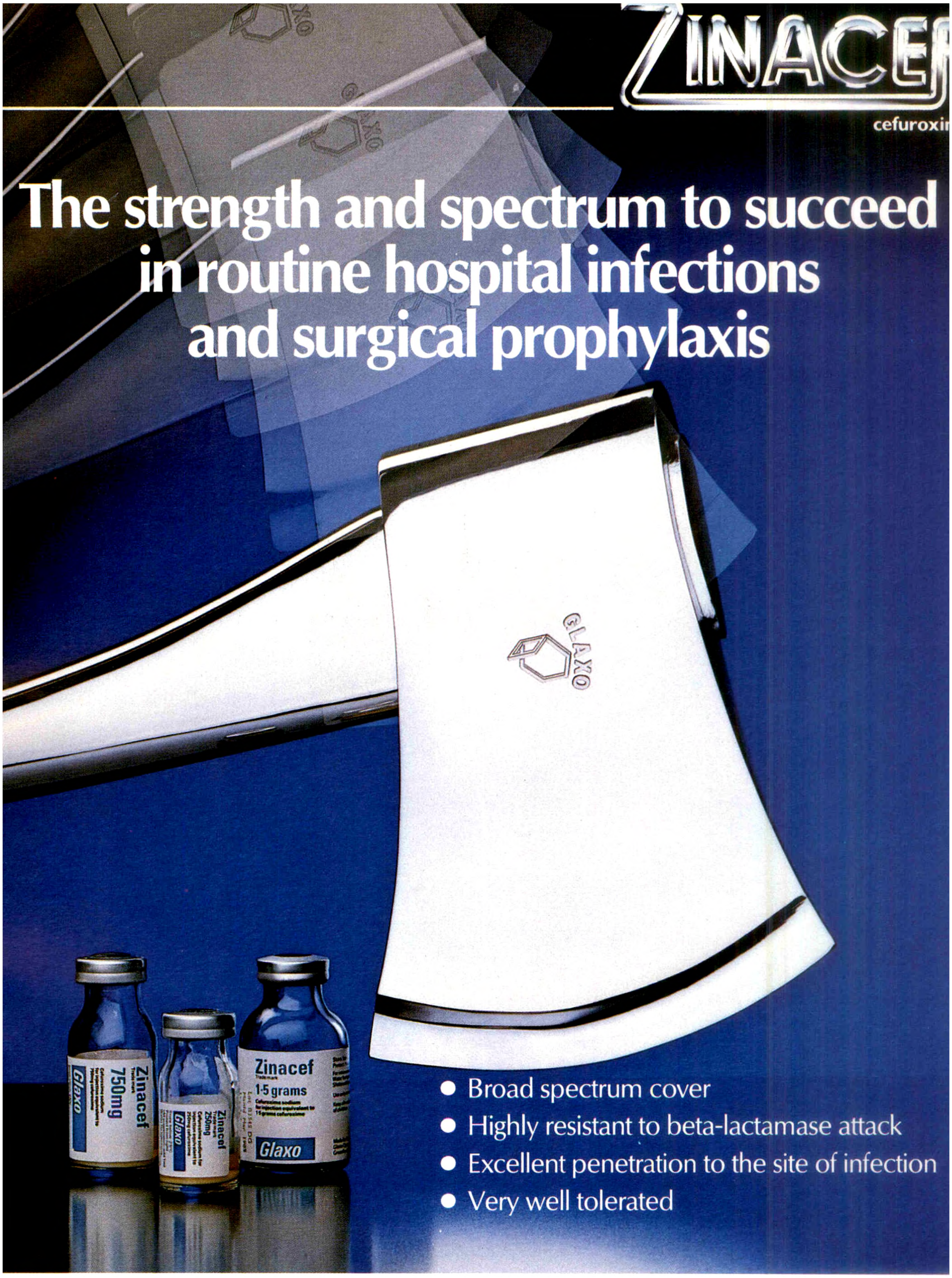

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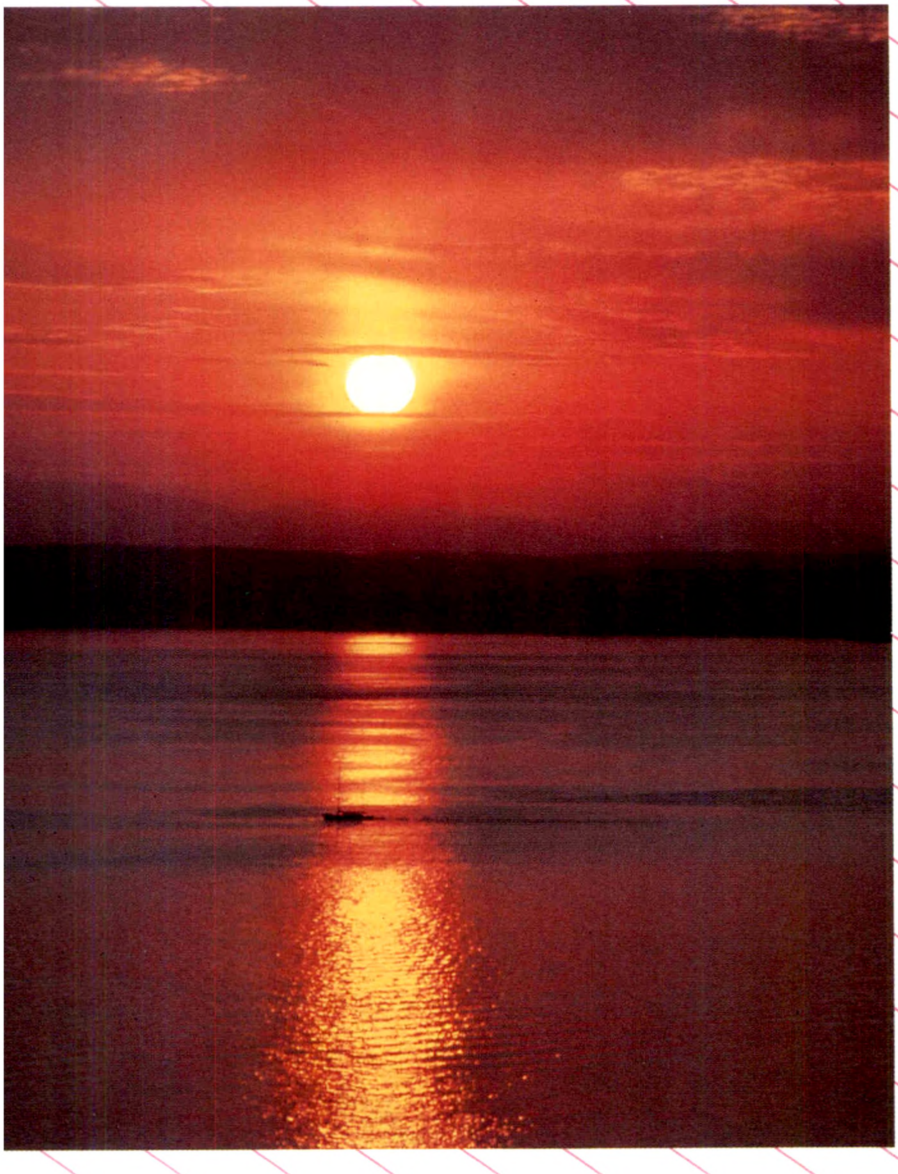

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Editorial

CAUTERY, FOLK REMEDIES, AND MAGIC

Traditional and folk medicine continue to be practiced widely in many developing countries, including Saudi Arabia. In this issue, Dr. Hugh G. Watts[1] discusses cutaneous cautery, which is widely used in Saudi Arabia. Over a period of 11 months, it was observed that 22% of the patients in the pediatric orthopedic clinic had undergone cauterization of the skin for various neurologic disorders. Cautery was generally sought when conventional medical treatment had failed. Interestingly, the parents' education did not appear to influence the decision to seek cautery.

Culture shapes the way in which distress is communicated and relieved. The relationship between the healer and the sufferer constitutes the first line of a placebo's therapeutic effect and is a potent force in recovery. Irrespective of the therapy rendered, the patient's basic trust in the healer is integral to the success of any treatment. In Saudi Arabia there are two forms of nonconventional medical therapy: traditional medicine and folk medicine.

Traditional medicine is a science based on experience, anecdotal observation, serendipity, and clinical observation. This represents the ancient medical profession, and its practice has been passed on over the centuries from one generation to another. Various forms of traditional healing methods are used widely throughout the third world. Noninvasive modalities include the use of herbal medicine and animal and insect substances.[2] Invasive modalities include cauterization and surgical procedures such as couching for cataract, and the use of bamboo sticks to tie the skin of eyelids to correct ptosis.

Folk medicine is a combination of religious beliefs, oral and written tradition, superstition, and habit. It is probably descended from priesthood and magic. Today in developing countries, folk medicine evokes elements of both divinity and sorcery. The saintly healer and the satanic dabbler in arcane arts are familiar figures in literature and legend. Passive reliance on the healer's magic demands a treatment that attenuates the sufferer's active participation.

Cutaneous cautery is a folk remedy that has gained popularity because of the self-limited nature of the diseases treated. Furthermore, cutaneous cautery inflicts pain and suffering to an otherwise passive patient. The dramatic effect achieved by this folk remedy in self-limited disorders has led to its wide popularity, but it is closer to the realm of magic than to traditional medicine.

The promulgation of folk remedies is due to a variety of factors which include a lack of confidence in modern medicine, the unavailability of conventional medicine in remote villages, the dramatic response in some of the psychosomatic or self-limited diseases, the influence of the grandparents, and the hope for a cure when conventional medicine has failed.

The persistence of folk remedy and especially cauterization to treat ailments such as poliomyelitis indicates the failure of conventional medicine in the treatment of these disorders.

There are currently many professions that have descended from the practice of folk and traditional healing methods. In Western countries, herbalists, bone setters, and traditional healers still exist.

Concerted efforts should be initiated to discourage the use of folk remedies and traditional healing methods. It is essential to promulgate correct notions regarding health and disease. The ultimate method to stop the practice of folk remedies and cutaneous cauterization mentioned by Watts[1] is to initiate public education campaigns, improve our clinical approach by improving our communication with the patient and his or her relatives (an art of healing), and continue in our research efforts to find new ways to diagnose and treat many of the chronic disorders.

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References

1. Watts HG. Cutaneous cautery (Al-Kowie): a study in a pediatric orthopedic clinic in central Saudi Arabia. Ann Saudi Med 1989;9(5):475-8.
2. Tabbara KF. Kermes-induced cicatrization of the conjunctiva. Ann Saudi Med 1986;6(4):233-6.

Original Articles

A COMPARATIVE STUDY OF HYPERGLYCEMIA IN DIFFERENT REGIONS OF SAUDI ARABIA

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أجريت دراسة أولية في مختلف مناطق المملكة العربية السعودية لتقصي تواتر حدوث فرط سكر الدم على الريق بين مواطني المملكة. بلغ التواتر الإجمالي في خيبر، والهفوف مع ما جاورها، والعلا ونجران وجازان نسبا تعادل ١٦,٥٪، ١٠,٩٪، ٩,٨٪، ٢,٤٪ و٨,٩٪ على التوالي. أشارت النتائج المستقاة من المتبرعين بالدم في الرياض إلى أن تواتر فرط السكر يبلغ نسبة ١,٤٪، في حين أن النتائج المستقاة من طلاب الجامعة كانت ٦,٣٪. وفي جميع ما سبق، باستثناء العلا، كانت النتائج في الذكور أعلى بشكل طفيف عنها في الإناث وكان الفرق ذا أهمية إحصائية. وبعد فقد شوهدت معظم حالات فرط سكر الدم في من بلغو الأربعين أو تجاوزوها. من الضروري إجراء دراسة وبائية بين المواطنين السعوديين لتقصي مدى انتشار مختلف أنواع السكري، وعوامله السببية وأعراضه السريرية والعوامل الوراثية وكذلك نسب المراضة والوفيات العائدة لداء السكري بين جمهرة المواطنين.

A pilot study was conducted in different regions of Saudi Arabia to estimate the frequency of fasting hyperglycemia in the Saudi population. In Khaybar, Hofuf and surrounding villages, Al-Ula, Najran, and Gizan, an overall frequency of 16.5%, 10.9%, 9.8%, 2.4%, and 8.9%, respectively, was encountered. In Riyadh, the results from blood donors showed a frequency of 1.4%, while the results from university students showed a frequency of 6.3%. In each case, except Al-Ula, the results in males were slightly higher than in females, and the difference was statistically significant. Furthermore, most of the cases with hyperglycemia were in the age range of 40 years or above. Epidemiologic studies are necessary in the Saudi population to determine the prevalence of different types of diabetes, etiologic factors, clinical manifestations, genetics, and morbidity and mortality associated with diabetes mellitus in this population.

Diabetes mellitus is one of the most common abnormalities that occurs in almost all populations of the world with variable prevalence.[1,2] It is a genetically and clinically heterogeneous group of metabolic disorders that share glucose intolerance in common.[3] There are several types of diabetes, and the two major classes are insulin dependent (type I) and noninsulin dependent (type II) diabetes.[3,4]

In Saudi Arabia, diabetes mellitus is believed to occur at a high rate, though few population surveys have been reported. In one study on the male population of Al-Kharj, 6.5% of the adult males above the age of 35 years were diagnosed as diabetic.[5] The prevalence increased to 11% in those between 55 and 64 years old and to 23% in those above 65 years of age. In a survey of 1018 patients referred to King Abdulaziz Hospital in Jeddah, 30% of the patients had diabetes mellitus.[6] In a comprehensive investigation on the population of the Western Region of Saudi Arabia, a prevalence of 4.95% and 4.3% was encountered in urban[7] and rural[8] populations, respectively. Other

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studies have shown that the majority of Saudi diabetics suffer from noninsulin-dependent (type II) diabetes,[9,10] though type I diabetes[11] and type II diabetes of the young (maturity-onset diabetes of the young)[12] have been reported in isolated cases.

We initiated a pilot study to determine the frequency of hyperglycemia in different regions of Saudi Arabia. This study was conducted by estimation of fasting blood glucose, and patients with glucose above the normal range were considered hyperglycemic. In this paper we present our results and compare the frequency in different regions of the country.

Materials and Methods

The regions screened during this study included Hofuf, Qatif and neighboring villages, Khaybar, Najran, Gizan, Al-Ula, and Riyadh. Field trips were made and fasting blood (5 mL) samples were collected by venipuncture in heparinized tubes from Saudi male and female university students, blood donors, and patients attending Ministry of Health hospitals and outpatient clinics for minor illnesses. No information on medication used by the individuals could be obtained. Analysis of blood glucose in whole blood was done immediately (within 10 minutes after collection) on fresh blood. Samples collected in different areas were analyzed by the Reflocheck-glucose kits on a Reflocheck reflectance photometer. The principle of this method is based on oxidation of glucose by glucose oxidase. Samples with known glucose level were included in every batch to maintain the accuracy of the instrument by constant standardization. The intra- and interassay coefficient of variation was 1.833 and 1.52, respectively.

Results

The samples with a blood glucose level of at least 7.2 mmol/L were grouped as hyperglycemic. Two subgroups were made, those with blood glucose level ranging from 7.2 to 10 mmol/L and those with blood glucose level over 10 mmol/L. The frequency of hyperglycemia encountered in the male and female Saudis in the different regions is presented in Table 1. The samples were further grouped on the basis of age, and these results are presented in Table 2. The statistical significance of results obtained between any two groups was determined using chi-square analysis

TABLE 1. *Prevalence of hyperglycemia in different regions of Saudi Arabia.*

	Sex	No. investigated	No. with hyperglycemia	Prevalence (%)
Gizan	M	407	48	11.8*
	F	314	16	5.1*
Total		721	64	8.9
Najran	M	264	8	3.0
	F	145	2	1.4
Total		409	10	2.4
Hofuf	M	315	46	14.6*
	F	334	25	7.5*
Total		649	71	10.9
Khaybar	M	166	28	16.9
	F	144	23	16.0
Total		310	51	16.5
Al-Ula	M	217	18	8.3*
	F	171	20	11.7*
Total		388	38	9.8
Riyadh University students	M	587	43	7.3*
	F	226	8	3.5*
Total		813	51	6.3
Blood donors	M	351	4	1.1

* Difference between the prevalence in the male and female populations is statistically significant.

TABLE 2. *Prevalence of hyperglycemia in different age groups in five regions.*

Area	Age group (y)	Prevalence (%) of Hyperglycemia	
		Male	Female
Gizan	< 20	11.9	2.0
	20 – 40	9.2	4.1
	> 40	16.7	14.6
Najran	< 20	1.1	0
	20 – 40	2.4	0
	> 40	5.9	9.1
Hofuf	< 20	5.6	7.3
	20 – 40	14.9	7.2
	> 40	26.0	8.4
Khaybar	< 20	13.3	10.9
	20 – 40	5.6	16.7
	> 40	20.4	19.6
Al-Ula	< 20	4.2	0
	20 – 40	6.2	1.2
	> 40	18.4	33.3

on 2×R contingency tables. A value of $P < 0.05$ was considered statistically significant.

Discussion

This pilot study was conducted to obtain information on the frequency of hyperglycemia in fasting Saudi subjects so that further plans can be made for a detailed study of the epidemiology and etiology of diabetes mellitus among the Saudi population. For the diagnosis of diabetes, the National Diabetes Data Group has recommended a fasting blood glucose level of greater than 7.8 mmol/L on two different occasions.[3] However, during the present study, a fasting blood glucose value at least 7.2 mmol/L was used as determining hyperglycemia. This was based on the result of an earlier study on Saudis, which reported a normal glucose range less than that reported for the Western population.[13]

The results of this study showed that the overall frequency of hyperglycemia was highest in the population of Khaybar, with a majority of the cases in the age range of more than 40 years. The difference between the male and female population was not statistically significant. In the population of the Eastern Province (Hofuf and surrounding areas), a frequency of about 10.9% was encountered, with a higher frequency among the male population ($P < 0.05$). The majority of the cases were in the age range of 40 years and above. The results from Gizan in the Southwestern Province showed a frequency of 8.9% with a higher frequency in the age group more than 40 years. The results from Al-Ula in the Northwestern Province was similar to those from Gizan. A considerably lower frequency of hyperglycemia was encountered in Najran in the Southwestern Province, and the majority of the cases were in the age group 40 years or more. This was in agreement with the results of Fatani and coworkers[7,8] and Bacchus and coworkers[5] in western and central Saudi Arabia, respectively. Riyadh results were based mainly on samples collected from blood donors who had the lowest frequency (i.e., 1.4%) and university students in the age range 18 to 30 years who had an overall frequency of about 6.3%. This difference could be due to the fact that the majority of individuals aware of their diabetic state do not contribute as blood donors, thus reducing the frequency of observed diabetes in the donor group.

The marked variation in the frequency of hyperglycemia in different regions of Saudi Arabia could be due to genetic causes. Genetics play an important role in the etiology of both type I and type II diabetes and familial concentration of the disease has been reported by several investigators.[14,15] In Saudis the high rate of consanguinity may account for the increased frequency of hyperglycemia in some regions, while in other regions where the abnormal genetic factor has not manifested itself, the frequency has remained low. This condition is equivalent to the wide variation observed in the frequency of other abnormal genes in the Saudi population.[16,17] In addition, environmental factors, dietary habits, and degree of physical activity may further contribute to the wide variation encountered in the different regions.

An interesting observation was a bimodal distribution of hyperglycemia among the male populations of Gizan and Khaybar. This indicated the presence of both juvenile-onset and maturity-onset diabetes at a higher prevalence in these regions, while in other areas, the prevalence in the persons under 20 years old was low and increased with age (Table 2).

In conclusion, this pilot study does not give any accurate estimation of the overall frequency of diabetes mellitus, but it does show that hyperglycemia occurs at a high frequency in the population of Saudi Arabia, and marked variability occurs among different areas. These results emphasize the need for detailed epidemiologic surveys in Saudi Arabia to determine the frequency of different types of diabetes, to identify the etiologic factors predisposing to this disease, and to identify the clinical manifestations, complications, morbidity and mortality associated with diabetes in the Saudi population. There is a definite need to initiate studies at a national level, to define the underlying causes for a high frequency of diabetes and to adopt measures to educate the general public and decrease the prevalence, morbidity, and mortality associated with this condition.

References

1. Mann JI, Pyorala K, Teuscher A, eds. Diabetes: epidemiological perspective. London: Churchill Livingstone, 1983:1-3.

2. West KM. Epidemiology of diabetes and its vascular lesions. New York: Elsevier, 1978:127-58.
3. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039-57.
4. Irvine WJ. Classification of idiopathic diabetes. Lancet 1977;1(8012):638-42.
5. Bacchus RA, Bell JL, Madkour M, Kilshaw B. The prevalence of diabetes mellitus in male Saudi Arabs. Diabetologia 1982;23(4):330-2.
6. Mira S, Fatani H, Baig MHA. A survey over a period of three years of glucose tolerance test at King Abdulaziz University Hospital, Jeddah (abstract). Proceedings of the 8th Saudi medical meeting, King Khalid Military Academy, Riyadh, 1983.
7. Fatani HH, Mira SS, El-Zubier AG. The prevalence of diabetes mellitus in urban Saudi Arabia. In: Niliyanant W, Vichayanrat A, Vannasaeng S, eds. Diabetes mellitus. Bangkok: Crystal House, 1985:8-16.
8. Fatani HH, Mira SA, El-Zubier AG. Prevalence of diabetes mellitus in rural Saudi Arabia. Diabetes Care 1987;10(2):180-3.
9. Kingston M. Dietary management of noninsulin dependent diabetes mellitus (abstract). Symposium on Gastroenterology, Riyadh, 1984.
10. Kingston M, Skoog WC. Diabetes in Saudi Arabia. Saudi Med J 1986;7(2):130-42.
11. Fatani H, Jan MY, Mira S, El-Zubier A. Ketoacidotic coma: a report of 92 consecutive patients admitted to King Abdul Aziz University Hospital (abstract). Proceedings of the 8th Saudi medical meeting, King Khalid Military Academy, Riyadh, 1983.
12. Kassimi MA, Khan MA. Maturity onset diabetes of youth in Saudi patients: is it a common problem? Saudi Med J 1981;2(3):146-8.
13. El-Hazmi MAF, Al-Faleh FZ, Al-Mofleh IA, et al. Establishment of normal "reference" ranges for biochemical parameters for healthy Saudi Arabs. Trop Geogr Med 1982;34:323-32.
14. Rotter JI, Rimoin DL. The genetics of glucose intolerance disorders. Am J Med 1981;70(1):116-26.
15. Simpson NE. Diabetes in the families of diabetics. Can Med Assoc J 1968;98:427-32.
16. El-Hazmi MAF. Haemoglobin disorders: a pattern for thalassaemia and haemoglobinopathies in Arabia. Acta Haematol 1982;68(1):43-51.
17. El-Hazmi MAF. Haemoglobinopathies, thalassaemias and enzymopathies in Saudi Arabia: the present status. Acta Haematol 1987;78(2-3):130-4.

CLINICAL USEFULNESS OF PREDICTED CREATININE CLEARANCE IN CANCER PATIENTS RECEIVING CISPLATIN THERAPY

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قيمنا الفائدة العملية لصيغة مستخدمة في التنبؤ بتصفية الكرياتينين، لدى أربعين مريضا بالسرطان أدخلوا على التوالي إلى المستشفى للعلاج الكيميائي بالسيزبلاتين. وجد بين مئة واثنتي عشرة عينة بول مجمع على مدار ٢٤ ساعة ترابط إحصائي جوهري بين المستوى القاعدي لتصفية الكرياتينين المتوقع والمقاس. وكان ذلك الترابط بين تصفية الكرياتينين المتوقع ذوي منسب السمنة المرتفع. وكان بالإمكان استخدام تصفية الكرياتينين المتوقع منفردا لتحديد جرعة السيزبلاتين المناسبة لدى ٨٥٪ من المرضى. أدى السيزبلاتين إلى خلل وظائف الكلى لدى سبعة مرضى (١٧,٥٪) ولم يكن لدى هذه الفئة الأخيرة أي ترابط هام بين تصفية الكرياتينين المتوقع والمقاس بالمقارنة مع من استمر أداء كلاهم في مستوى طبيعي أو شبه طبيعي. ارتبط ارتفاع كرياتينين المصل، في سلسلتنا هذه، ارتباطا وثيقا بانخفاض أداء كبب الكلية. توحي هذه النانئج بأن تصفية الكرياتينين المتوقع تشكل بديلا مقبولا وموثوقا وغير مكلف للقياس المعتاد لتصفية الكرياتنين في تقييم وظيفة كبب الكلية وتحديد الجرعة المناسبة من السيزبلاتين، لكن يجب أن يقتصر استخدامه على المرضى غير البدينين ومن يتمتعون بأداء وظيفي كلوي مستقر.

We assessed the practical usefulness of a formula known to predict creatinine clearance in 40 consecutive cancer patients admitted for cisplatin chemotherapy. Of 112 24-hour urine collections, a statistically significant correlation was found between base-line predicted creatinine clearance (PCC) and measured creatinine clearance (MCC). A higher degree of correlation was established between PCC and MCC for patients with low and intermediate adiposity indexes in contrast with those who have a higher index. Using the PCC alone would have allowed a proper cisplatin dose determination in 85% of patients. Seven patients (17.5%) showed cisplatin-induced renal impairment. In the latter subgroup, no significant correlation was found between PCC and MCC, in contrast to those who maintained a normal or near-normal renal function. In our series, rising serum creatinine correlated well with the fall in glomerular function. Those results suggest that PCC is an acceptable, reliable, and inexpensive alternative to MCC in the assessment of glomerular function and determination of the proper dose of cisplatin. Its use, however, should be restricted to nonobese patients and those with stable renal function.

In clinical practice, despite its associated inherent errors and variability, measured creatinine clearance (MCC) provides a commonly used estimate of the glomerular filtration rate (GFR).[1] Variability of the procedure is usually due to inaccuracy of the 24-hour urine collection,[2] alteration in dietary protein intake,[3-5] or the effect of age.[6] In addition to being time-consuming and costly, assessment of GFR using MCC often lacks reproducibility.[7,8]

A formula has been developed to predict creatinine clearance from serum creatinine.[9] The

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derivation was based on studying a large number of patients and comparing their predicted creatinine clearance (PCC) with the means of two 24-hour MCC in another large sample. This method was recently evaluated to study its accuracy, reproducibility, and its application in cisplatin dose determination in cancer patients.[10] The procedure was found to be accurate and more reproducible than the traditional MCC method. However, in the latter study,[10] several patients were allowed to contribute more than one observation to the pool of data regressed. The latter practice may violate the assumption of statistical regression where all the points in the array of data must be independent samples.[11] Furthermore, authors did not test the validity of the formula in certain subcohorts, such as obese patients or those with cisplatin-induced progressive deterioration of their renal function. The PCC formula is known to be accurate only in patients with stable renal function who are not massively obese or edematous.[12]

In our study we examined the clinical usefulness of the PCC and its practical utilization for patients receiving cisplatin and categorized according to their adiposity index and their various degrees of renal function.

Materials and Methods

Forty consecutive previously untreated patients admitted to our hospital for cisplatin administration were considered eligible for the study. All adult cancer patients between 15 and 75 years old who were receiving cisplatin were included. To be eligible, patients needed a minimum life expectancy of 3 months and normal base-line renal function (serum creatinine less than 150 μmol/L and accurate MCC greater than 1.67 mL/s). There were 23 males and 17 females. Their mean age was 41 ± 16.1 years (range, 17 to 75 years). Male patients had squamous cell carcinoma of the head and neck (13 patients), bronchogenic carcinoma (seven patients), and genitourinary carcinoma (three patients). Of the eligible females, nine had ovarian carcinoma, five had head and neck neoplasm, two had bronchogenic carcinoma, and one had abdominal mesothelioma. All 24-hour urine collections were done as inpatients. Creatinine clearance was measured by a standard formula (MCC).[1] Determination of urine and serum creatinine was done by the Jaffe kinetic method.[13] For each MCC, a PCC was calculated for male patients according to the following formula[9]: PCC $= (140\text{-age}) \times \text{weight in kg}/72 \times \text{serum creatinine}$ (μmol/L). For female patients, the result was multiplied by 0.85.

Measured creatinine excretion of less than 10 mg/kg/d was used as an indicator for inaccuracy and inadequacy of the 24-hour urine collection.[9,10]

In all patients, cisplatin was administered as intravenous infusion over 6 hours in day 1 of therapy together with a uniform procedure for hydration both before and after chemotherapy concomitant with osmotic diuresis using mannitol. Urine output was maintained above 100 mL/hour by adjusting the intravenous fluid rate and, if necessary, with the help of loop diuretics. Most patients received cisplatin together with other anticancer medications. However, none of the patients received other nephrotoxic agents concomitantly with cisplatin. Cycles were repeated at 3-week intervals. Cisplatin was given as 100 mg/m^2, 75 mg/m^2, and 50 mg/m^2 for MCC of greater than 2.00 mL/s, 1.67-1.99 mL/s, and 0.83 to 1.66 mL/s, respectively. Therapy was deferred if MCC was below 0.83 mL/s.

As values for both MCC and PCC demonstrated a normal distribution, Pearson's correlation coefficient was used to estimate the correlation between the two parameters.[14] A P value of < 0.05 was considered significant.

Results

All 24-hour urine collections were done as inpatients with an average hospital stay of 2 days (range, 1 to 6 days) for measuring creatinine clearance prior to the administration of anticancer therapy. Collections that were considered inaccurate based on creatinine excretion of less 10 mg/kg/d were repeated. Of 125 collections, 31 (25%) were regarded as incorrect and repeated. Only correct collections (112 collections) were considered for further analysis. The mean ± SD for MCC and PCC was 1.87 ± 0.15 mL/s and 2.03 ± 0.28 mL/s, respectively. No statistically significant difference was noted between those two means. Studying the correlation between base-line MCC and PCC for 125 pairs of observations revealed a significant positive correlation ($r = 0.632$, $P = 0.0005$). The latter correlation was still significant ($r = 0.547$, $P = 0.001$), even if only one pair of observations (initial MCC and PCC) was used in the analysis for each patient.

The correlation between MCC and PCC based on each patient's adiposity index (weight/height^2) was also analyzed (Table 1). A lack of correlation between the two parameters was noted among patients with high adiposity index indicating a poor predicting function for PCC in that category of patients.

We also assessed the practical application of PCC in determining cisplatin dose. In all 40 patients, utilization of base-line PCC only would have resulted in administration of the actual dose given based on the MCC in 34 patients (85%), overdosage in five (12.5%), and underdosage in one (2.5%). On the other hand, taking the adiposity index into consideration would have allowed an accurate dose calculation in 16 (100%), 12 (92%), and six (55%) of patients in the low, intermediate, and high adiposity index categories, respectively. In the high category, all erroneous estimations were due to overdosage.

After an average of three courses of cisplatin treatment (range, 1 to 6 courses), seven patients (17.5%) showed more than 20% deterioration in their pretreatment serum creatinine levels and/or their MCC. In only those seven patients, we noted a significant intrapatient variability in the MCC and PCC from course to course. Furthermore, in those patients, a negative correlation was found between rising serum creatinine and falling renal function. While a lack of correlation was noted between MCC and PCC in that subset of patients with unstable renal function, the significant correlation between the two parameters was still observed for those who maintained normal renal function (Table 2).

Estimation of Pearson's correlation between MCC and PCC demonstrated a significant correlation between the two parameters, irrespective of sex.

TABLE 1. *Correlation between base-line MCC and PCC in 40 patients based on adiposity index.*

No.	Adiposity index	Correlation coefficient	*P* value
16	< 2.25 (low)	0.834	< 0.0001
13	2.25–2.49 (intermediate)	0.610	0.027
11	> 2.5 (high)	0.532	0.092

TABLE 2. *Correlation between latest MCC and PCC in 40 patients based on changes in renal function.*

Renal function	No.	Correlation/ coefficient	*P* value
Stable	33	0.501	0.0029
Impaired	7	0.327	0.4740

Discussion

While MCC is the most practically used method for GFR determination, the procedure is associated with certain disadvantages, such as its variability and low reproducibility, its cost, and the time involved.[2-8] The expense of MCC is mainly attributed to the need for hospital admission to ensure accurate urine collection. In our series, the average hospital stay per admission solely for MCC determination was 2 days with a range of 1 to 6 days. Despite hospitalization, 25% of all 24-hour urine collections were considered inaccurate. The latter figure is similar to that of 35% reported from another series.[10] For the above reasons, some clinicians have raised doubts about the usefulness of MCC in clinical medicine,[8] while others have abandoned the procedure prior to cisplatin administration.[15]

In a recently published trial,[10] use of the PCC formula showed a significant correlation with MCC for all collections ($r = 0.684$) and higher correlation for collections that were considered accurate ($r = 0.922$). In the latter study, correlation was not evaluated based on adiposity index or levels of renal function. Furthermore, several observations from the same subject were used for the analysis. The potential error involved with this practice is well known.[11] In our study, a significant, though lower, correlation was found between MCC and PCC ($r = 0.547$). However, higher degrees of correlation were obtained from patients with low or intermediate adiposity indexes, as compared to obese patients. For patients with low, intermediate, and high adiposity indexes, PCC predicted 70%, 40%, and 28% of the MCC's variability, respectively. Those data confirmed the limitation of the PCC procedure in obese subjects.[12] The procedure, however, was of help in determining the proper dose of cisplatin in 85% of patients. The latter figure is similar to that of 82% reported recently.[10] Taking the adiposity index into consideration improved the accuracy of PCC in estimating cisplatin dose for those with low or intermediate indexes compared to those who were obese. In the latter group, use of PCC alone would have resulted in overdosage in almost half of the patients.

Studying data for those patients who developed cisplatin-induced renal impairment has revealed useful information. In our study, a negative correlation was found between rising serum creatinine and falling renal function as determined by MCC or PCC. A similar observation was also noted in 31 patients studied for the evaluation of the long-term effect of cisplatin on renal function.[16] In fact, measuring serum creatinine might more accurately reflect the change in glomerular function than the frequently variable MCC.[8,13] However, PCC in our study has not been able to predict those who would develop cisplatin-induced renal toxicity. Therefore, rising serum creatinine should be considered as an indication that use of the PCC formula might give an erroneous estimate of GFR and improper cisplatin dose determination.

In conclusion, there is still a need for a practical, reliable, reproducible, inexpensive, and rapid procedure to accurately predict GFR in most cancer patients receiving cisplatin. The PCC formula is an inexpensive and useful tool for the evaluation of GFR and determination of the proper cisplatin dose. Its use, however, should be restricted to nonobese patients and to those who maintain stable renal function during therapy as indicated from serum creatinine. On the other hand, the lack of correlation between PCC and MCC in obese patients and in those with progressive impairment of kidney function might be due to the inaccuracy and variability of MCC. Determination of GFR using the PCC formula deserves further assessment against methods that are more accurate than MCC, such as ^{51}Cr-EDTA.[17] Design of such a study is now underway.

References

1. Brenner BM, Ichikawa I, Deen WM. Glomerular filtration. In: Brenner BM, Rector FC, eds. The kidney. Philadelphia: WB Saunders, 1981:289-327.
2. de Wardener HE. The kidney. Edinburgh: Churchill Livingston, 1985:40-1.
3. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307(11):652-9.
4. Bosch JP, Saccaggi A, Lauer A, et al. Renal functional reserve in humans: Effect of protein intake on glomerular filtration rate. Am J Med 1983;75(6):943-50.
5. Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 1962;32:65-79.
6. Rowe JW, Andres R, Tobin JD, et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J Gerontol 1976;31(2):155-63.
7. Morgan DB, Dillon S, Payne RB. The assessment of glomerular function: creatinine clearance or plasma creatinine? Postgrad Med J 1978;54(631):302-10.
8. Payne RB. Creatinine clearance: a redundant clinical investigation. Ann Clin Biochem 1986;23:243-50.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.
10. Davila E, Gardener LB. Clinical value of the creatinine clearance before the administration of chemotherapy with cisplatin. Cancer 1987;60(2):161-4.
11. Glantz SA. Primer of biostatistics. New York: McGraw-Hill, 1981:181.
12. Reidenberg MM. Kidney function and drug action (editorial). N Engl J Med 1985;313(13):816-8.
13. Spencer K. Analytical reviews in clinical biochemistry: the estimation of creatinine. Ann Clin Biochem 1986;23:1-25.
14. Chase CI. Elementary statistical procedures. New York: McGraw-Hill, 1984:127-59.
15. Soloway MS, Einstein A, Corder MP, et al. A comparison of cisplatin and the combination of cisplatin and cyclophosphamide in advanced urothelial cancer. Cancer 1983;52(5):767-72.
16. Fjeldborg P, Sorensen J, Helkjaer PE. The long-term effect of cisplatin on renal function. Cancer 1986;58(18):2214-7.
17. Brochner-Mortensen J, Rodbro P. Comparison between total and renal plasma clearance of ^{51}Cr-EDTA. Scand J Clin Lab Invest 1976;36:247-9.

A 12-MONTH AEROBIOLOGICAL SURVEY OF POLLEN IN RIYADH

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أظهرت دراسة على مدى ١٢ شهرا على الأحياء الهوائية المنتشرة في غبار الرياض أن لانتشار غبار الطلع ذروتين، ذروة الربيع في شهر مارس وأبريل ومايو. وذروة الخريف في شهر أكتوبر. تم تسجيل أعداد كبيرة من أجناس النباتات، بما في ذلك كل من الأنواع المحلية والمستجلبة. كانت سحب الغبار تحجب لقاحات النباتات أحيانا أو تتلفها، فتعيق التعرف عليها. أظهر عد غبار الطلع في متر مكعب على مدى ساعة واحدة إبان الذروة وجود ١٣ نوعا في عد واحد على الأقل وأغلب هذه الأنواع تجاوزت في مرات متعددة الحد المتعارف عليه سريريا وهو من ١٠ إلى ٢٠ حبة في كل متر مكعب. كانت الأنواع مرتبة حسب الأكثر شيوعا إلى الأقل تواردا تشمل نباتات رجل الوزة (والتي تشمل شحم العشب)، الحشائش، نباتات لسان الحمل، نبات الشيبة والعنبرية. كانت الحشائش ونباتات رجل الوزة تفرز اللقاحات على مدى ١١ إلى ١٢ شهرا في العام. نعرض الآن تقويما فصليا لغبار الطلع الأصفر النباتي كدليل لمستأرجات محتملة في مختلف الأوقات خلال العام.

A 12-month aerobiological survey of pollen in Riyadh showed a double peak of pollen grains, a spring peak in March, April, and May and an autumn peak in October. A large number of genera were recorded, including both indigenous and imported varieties. Dust clouds at times obscured or damaged pollen grains, hindering recognition. Peak pollen counts per cubic meter in 1 hour showed that 13 genera on at least one occasion and most of these on many occasions exceeded the clinically significant levels of 10 to 20 grains per cubic meter. Genera in order from the most to least common were Chenopodiaceae (which includes the weed fat hen), grasses, plantain, *Artemisia*, and *Ambrosia*. Grasses and Chenopodiaceae released pollen 11 to 12 months of the year. A seasonal pollen calendar is presented as a guide to likely allergens at different times of the year.

Airborne pollen and fungal spores are common triggers of type I IgE-mediated allergic reactions in patients with rhinitis and bronchial asthma. The seasonal appearance of various pollen, such as ragweed and grasses, signals the onset of hay fever or pollinosis seasons. Essential to a diagnosis of pollen or mold-induced nasal or respiratory symptoms is clear information on which pollen or spores are present and at what times of the year.

While allergy skin-testing is widespread as a diagnostic tool in the Kingdom, an accurate chart of the seasonal appearance of pollen and fungi has not been reported for the different regions of Saudi Arabia.[1] To rectify this deficiency, a three-city aerobiological survey has been set up in Riyadh, Jeddah, and Al-Khobar.

This paper presents the results of a full year's survey of pollen in the Riyadh atmosphere delineating the various botanical families likely to contribute to inhalant allergies in the Riyadh region. Aero-allergological information on fungal

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spores has been published as a separate communication.[2]

Methods

As described in a previous communication,[3] air was sampled on a continuous 24-hour basis with a Burkard 7-day volumetric spore trap mounted on the roof of a two-story building at King Faisal Specialist Hospital and Research Centre (KFSH & RC). At weekly intervals the collecting tape was removed and mounted on microscope slides, and the pollen were identified and counted in bands corresponding to hourly samples throughout the day.

Based on the air intake of the spore trap, a series of quantitative values were calculated for each pollen group including hourly, mean weekly, and mean monthly levels expressed as pollen grains per cubic meter of air sampled.

To aid in the identification of pollen, the study was supported by the collection of over 100 native plant species during their flowering season, and their pollen were mounted and stored as a reference set.

For periods of 3 months or more, a second spore trap was run in conjunction with the first trap, at King Abdulaziz University Hospital (KAUH) in an old, established central area of Riyadh, and later at King Khalid University Hospital (KKUH) in a zone of extensive, but newly planted gardens on the outskirts of the city.

Results

Figure 1 shows total mean pollen levels recorded as the mean monthly count per cubic meter over the 13-month period from November 1986 through November 1987. Two pollen peaks are clearly defined, the first spring peak in March, April, and May as growth recommences after a short winter, and the second higher autumn peak in October, as the temperature falls from the heights of summer.

Many species contribute to the seasonal peaks, with both grasses and Chenopodiaceae as the largest groups in spring and Chenopodiaceae in autumn. When the maximal peak levels were compared by hour, sharp peaks or pollen clouds were seen with counts up to 10 times higher than the monthly mean. Figure 1 summarizes the maximum peak counts each week showing hourly levels as high as 300 grains per cubic meter. At the time of each peak, however, neither of these two species represented more than 25% of the pollen at that time.

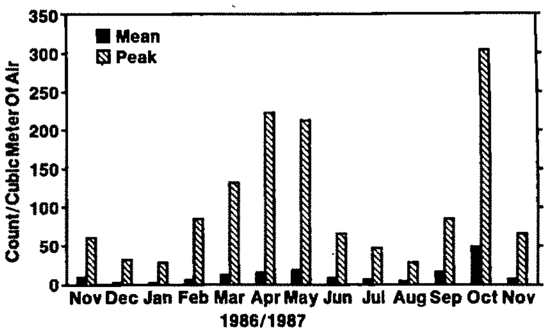

FIGURE 1. Mean and peak pollen levels.

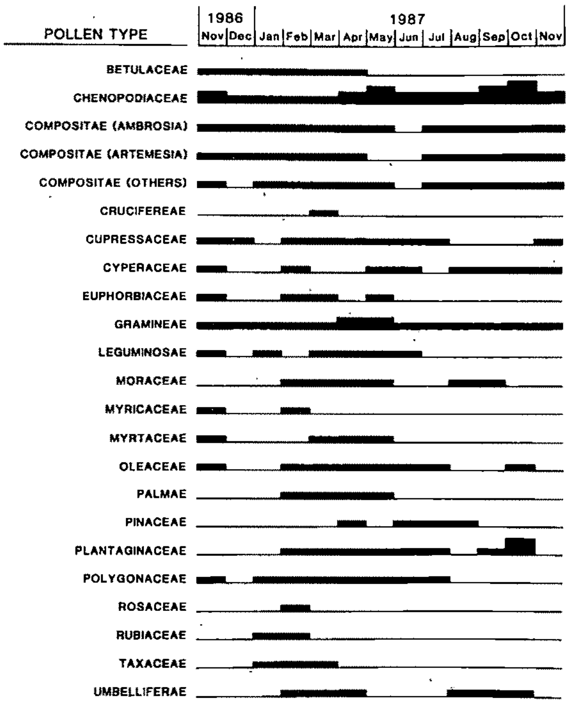

FIGURE 2. Semiquantitative guide to seasonal presence of pollen genera.

Up to 50% of pollen at any one time could not be identified because the grains were so damaged or obscured by dust impaction. Occasionally, pollen could not be identified, as they did not correspond to any reference material. Assuming that the pollen damage or obscuring was a random event, the identified grains would be present twice as commonly as recorded. The many other genera contributing pollen are presented with a semiquantitative guide to their pollen season on Figure 2. Each pollen type contains representatives from a number of different species, and some of the common ones are listed in Table 1.

Pollen of one genus was commonly present in trap samples from KFSH & RC and KKUH but to date has not been identified. Further attempts are in progress to label this pollen which is clearly a ubiquitous plant in the region.

Plotting the hourly counts showed the impact of sudden changes in meterological factors such as humidity, wind speed, and direction. From 2 PM to midnight on 24 October 1987, hourly total pollen count averaged 13 grains per cubic meter. After midnight, the hourly count rose to over 100, peaking at 8 AM at 304 grains per cubic meter in 1 hour. In general, peak pollen clouds during autumn occurred in the early morning, usually persisting 5 to 6 hours. In springtime, the peaks, especially grasses, peaked later in the morning. For example, on 25 April 1987, the average total pollen count was 12 grains per cubic meter each hour between midnight and 10 and 11 AM. The spring peak was commonly shown, lasting 2 to 3 hours only.

To assess the relative clinical importance of the different pollen genera, the peak hourly count was recorded during each month and rated on the following scale: 1-15 grains per cubic meter = 1; 16-30 = 2; 31-45 = 3; and above 45 = 4. Adding the counts for the 2 months provided a rough index of maximal pollen levels and their persistence through the year. Table 2 presents these data ranking the pollen from the most to least common and listing the maximal hourly count during the year. While Chenopodiaceae, grasses, plantains, and *Artemisia* were the most common pollens, all 13 groups listed have, at one time during the year, produced hourly pollen counts above 10 grains per cubic meter.

A close examination of the hourly peak throughout the year shows that pollen from the Chenopodiaceae family have exceeded 10 grains per cubic meter in at least 1 hour during every month. Similarly, grasses were persistent throughout the year with a continuous background release failing in only 1 month, January, to achieve a peak of 10 grains per cubic meter. Other genera showed pollen for a few weeks each, such as Palmae, including date palms, whose pollen was present only in March, April, and May.

TABLE 1. *Families of pollen detected on Burkard spore slide and representative species found in the area.*

Families of pollen detected	Representative species found in the area
Compositae	*Ambrosia, Artemisia*
Other Compositae	*Launaea capitata, Pulicaria glandulosa*
Chenopodiaceae	*Atriplex leucoclada, Hammada elegans*
Cruciferae	*Farsetia depressa, Diplotaxis harra*
Cupressaceae	*Juniperus procera, Cupressus semipervirens*
Cyperaceae	*Cyperus conglomeratus, Cyperus rotundus*
Euphorbiaceae	*Ricinus cummunis, Euphorbia retusa*
Gramineae	*Cynodon dactylon, Stipagrostis plumosa*
Leguminosae	*Acacia gerrardii, Prosopis farcta*
Moraceae	*Morus nigra, Ficus carica*
Myricacae	*Myrica salicifolia*
Myrtaceae	*Myrtus communis, Eucalyptus rostrata*
Oleaceae	*Jasminum florbunum, Olea chrysolohylla*
Palmae	*Hyphaene thebaica, Phoenix dectylifera*
Pinaceae	*Pinus* spp.
Plantaginaceae	*Plantago cylindrica, P. ciliata*
Polygonaceae	*Rumex vesicarius, Calligonum comosum*
Rosaceae	*Amygdalus arabica, Rosa abyssinica*
Rubiaceae	*Rubus arabicus*
Umbelliferae	*Daucus syrticus, Pimpinella cretica*

TABLE 2. *Pollen type, frequency, and peak response.*

Rank order	Pollen	Rate score*	Maximum level per cubic meter	Month of peak
1	Chenopodiaceae	36	148	October
2	Graminae (grasses)	21	52	May
3	Plantaginaceae (plantain)	14	81	October
4	*Artemisia*	13	24	November
5	*Ambrosia*	11	14	October
6	Other Compositae	11	14	May
7	Cyperaceae	10	129	May
8	Oleaceae	9	29	February
9	Betulaceae	8	19	November
10	Cupressaceae	8	19	March
11	Palmae	5	33	March
12	Polygonaceae	5	24	May
13	Leguminoseae	5	19	April

* Rate score calculated on 12-month cumulative scores for each month, maximum grains per cubic meter in 1 hour rated; 1–15 = 1; 16–30 = 2; 31–45 = 3; and > 45 = 4.

Artemisia and *Ambrosia* constitute two very allergenic genera, known as mugworts and ragweeds, respectively. Both genera released pollen throughout the year at low levels rising to peaks in autumn when counts frequently exceed 10 grains per cubic meter.

Comparison between readings at the KFSH & RC and the other two sites showed some differences, with values at KAUH generally low and at KKUH comparable with KFSH & RC recordings. Mean monthly total pollen counts per cubic meter for KFSH & RC and KAUH, respectively, in May were 18.8 and 8.5; June, 8.8 and 4.7; July, 6.8 and 3.6; and August, 4.7 and 4.6. The same values for KFSH & RC and KKUH, respectively, were September, 17 and 23.5; October, 50.2 and 44.7; and November, 10.1 and 3.4.

Discussion

The first comprehensive aerobiological survey of pollen in Saudi Arabia answers a number of questions by identifying the various genera of pollen, defining their seasonal appearance, and measuring their atmospheric concentration.

Clinical experience in recent years clearly emphasizes the real problem of rhinitis and bronchial asthma in the Kingdom; in both conditions inhalant allergic material is a well-recognized trigger. Davies and Smith,[4] studying the relation between pollen counts and severity of hay fever seasons in the United Kingdom, concluded that ambient grass pollen levels of 20 grains or more per cubic meter were associated with overt symptoms in virtually every specific-sensitive subject. Solomon and Mathews[5] placed the relevant level for ragweed pollen at 9 grains per cubic meter.

When the results of the present Riyadh pollen survey are examined in light of the adverse clinical consequences of generic pollen counts per cubic meter of 10 to 20 or above (and ground level readings will be substantially higher than the two-story levels recorded here), then the clinical impact is clear. Thirteen different genera or families produced pollen clouds exceeding 10 grains per cubic meter at least once, but usually on many occasions during the year. Grasses and Chenopodiaceae each achieved clinically significant levels (10 or above) 11 and 12 months of the year, respectively, rising dramatically to their spring and autumn peak of 50 or 100 or more. When these values are adjusted upward by as much as 100% to compensate for the large number of pollen grains counted but not identified, as they were either damaged or obscured by sand, the clinical impact is further emphasized.

Examination of the pollen season for the different genera provides data of clinical value when trying to relate patient symptoms to potential pollen exposure. Palm trees and members of the Cyperaceae family (perennial or annual herbs which grow widely in the Kingdom) exhibit short, sharp seasons. In contrast, grasses, despite the springtime peak, are releasing pollen throughout the year when the high ambient temperature combined with regular irrigation encourage year-round growth.

Of major importance for further study is the contribution of pollen from the genera *Artemisia* and *Ambrosia* with their potent allergenic lineage. Many species of each grow in Saudi Arabia, and as their pollen reaches peaks of 10 to 20 grains per cubic meter during 4 to 5 months of the year, recorded at two stories above the city, then much higher exposure would occur at ground level near these desert plants. No information is available concerning their allergenic cross-reactivity with the traditional ragweed and mugworts of the United States and Europe.

Leguminosae include *Acacia* and *Prosopis*, and both local and imported varieties have been extensively planted in Riyadh. Pollen grains reach levels of 10 or more per cubic meter during the springtime months, and very high levels of exposure would be expected adjacent to these trees.

The double pollen season, spring and autumn, is not unique, having been described in Arizona[6] and India.[7] But it represents a significant contrast to pollen patterns in temperate climates. The only other formal attempt to record pollen quantitatively in the region was reported in 1969 from Kuwait.[8] Davies showed Chenopodiaceae were by far the most common pollen, contributing 66% of total count, while grasses reached only 3% of total pollen, only occasionally reaching levels of 10 grains per cubic meter, a contrast from the picture in Riyadh in 1987. He also identified *Artemisia* and *Prosopis* in low numbers. From the same region, Wilkinson[9] showed a double inhalant allergy season from patient consultations.

The clinical correlation of this study with skin testing allergic patients is almost complete and will be the subject of a separate communication.

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References

1. Sorensen H, Ashoor AA, Maglad S. Perennial rhinitis in Saudi Arabia: a prospective study. Ann Allergy 1986;56:76-80.
2. Hasnain SM, Al-Frayh AR, Harfi H, et al. Seasonal periodicities of fungal allergens in the atmosphere of Riyadh. Ann Saudi Med 1989;9(4):337-43.
3. Al-Frayh AR, Hasnain SM, Wilson JD, Harfi H. Fungal allergens in the atmosphere of Riyadh: a preliminary communication. Ann Saudi Med 1988;8(4):248-51.
4. Davies RR, Smith LP. Forecasting the start and severity of the hay fever season. Clin Allergy 1973;3:263-7.
5. Solomon WR, Mathews KP. Aerobiology and inhalent allergens. In: Middleton E, Reed CE, Ellis EF, eds. Allergy: principles and practice. 2nd ed. St. Louis: CV Mosby, 1983:1143-1202.
6. Dworin M. Allergy in the Sonoran desert (abstract). Excerpta Medica 1967;144:41.
7. Singh AB, Babu CR. Survey of atmospheric pollen allergens in Delhi: seasonal periodicity. Ann Allergy 1982;48:115-22.
8. Davies RR. Spore concentrations in the atmosphere at Ahmadi, a new town in Kuwait. J Gen Microbiol 1969;55:425-32.
9. Wilkinson WM. Development of allergy in the desert. J Trop Med Hyg 1964;67:16-8.

SUSCEPTIBILITY OF PATHOGENIC BACTERIA TO AMOXICILLIN/CLAVULANIC ACID (AUGMENTIN) AT A REFERRAL HOSPITAL

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تم فحص ما مجموعة ٩٥٧ ذرية من البكتيريا المعزولة من العينات السريرية في المختبر لتحديد فعالية مزيج الأموكسيسيلين/حامض الكلافولانيك (أو غمنتين). ثبط هذا المزيج نمو ما نسبته ٦٧٪ من ذراري الأمعائيات البالغ عددها ٥٣٨، و٩٣٪ من ذراري العنقودية الذهبية (١٧٤)، وجميع المكورات المعوية المعزولة (٤٨)، في حين قاومته جميع ذراري الزائفة الزنجارية والزائفة المتألقة والأنتروباكتر والسراتية والشيغلة الفلكسنرية (١٥٦). كما أظهر المزيج نشاطا أكبر ضد الاشريكية القولونية والكلبسيلة الرئوية ونوع المتقلبة والعنقوديات بالمقارنة مع الأمبيسيلين.

A total of 957 strains of bacteria isolated from clinical specimens were tested in vitro to determine the efficacy of amoxicillin/clavulanic acid (Augmentin). Sixty-seven percent of the 538 strains of Enterobacteriaceae, 93% of 174 *Staphylococcus aureus*, and all the 48 isolates of enterococci were inhibited by Augmentin. All the 156 strains of *Pseudomonas aeruginosa, P. fluorescens, Enterobacter, Citrobacter, Serratia*, and *Shigella flexneri* were resistant to Augmentin. Augmentin showed considerably increased activity against *Escherichia coli, Klebsiella pneumoniae, Proteus* species, and staphylococci when compared with ampicillin.

Bacteria acquire resistance to penicillin by several different mechanisms. These include alteration of autolysins, transition to L-forms, development of impermeability, and production of enzymes that inactivate the drug.[1-4] Synthesis of beta-lactamase is the principal mechanism of penicillin resistance in bacteria. Until recently, use of many penicillins was precluded for the treatment of infections caused by beta-lactamase producers. About a decade ago, Reading and Cole[5] reported that clavulanic acid, produced by the fermentation of *Streptomyces clavuligerus*, had the ability to inactivate irreversibly a wide variety of beta-lactamases. This led to the development of Augmentin, which contains two parts of amoxicillin trihydrate to one part of clavulanate potassium (the potassium salt of clavulanic acid). (Sensitivity discs and formulary tablets of amoxicillin and clavulanate are prepared in a 2:1 ratio, but oral suspensions have a ratio of 4:1, respectively.)

In vitro studies in the United States and Europe have shown Augmentin to possess increased activity against Enterobacteriaceae, staphylococci, and enterococci.[6-14] Although the drug has been available in other countries for some time, it was introduced in Saudi Arabia only recently. In this paper we report the activity of Augmentin against pathogenic bacteria that have been isolated from clinical specimens in a tertiary care referral center in Saudi Arabia where the bacterial isolates are more resistant to commonly used antimicrobial agents than in the United States.

Materials and Methods

Antimicrobial Agents

Agar diffusion tests were performed using com-

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mercially prepared antibotic disks. The antibiotic content of the disks was 10 μg for ampicillin, colistin, gentamicin, and tobramycin; 15 μg for erythromycin; 30 μg for Augmentin, amikacin, cephalothin, chloramphenicol, tetracycline, and vancomycin; 1.25 μg/23.75 μg for trimethoprim-sulfamethoxazole; 10 units for penicillin G; 100 μg for carbenicillin; and 1 μg for oxacillin. The disk contents used are those recommended by the National Committee for Clinical Laboratory Standards[15] for which interpretive data have been established.

Bacteria

Clinical specimens were tested over a 6-month period at the King Faisal Specialist Hospital and Research Centre, a 470-bed referral medical and surgical hospital in Riyadh. Microorganisms were identified by conventional methods described in the *Manual of Clinical Microbiology*.[16] These bacteria consisted of strains of Enterobacteriaceae, strains of *Pseudomonas aeruginosa*, strains of *Staphylococcus aureus* and *Streptococcus* species. The isolates were obtained from cultures of blood, respiratory secretions, urine, wounds, and miscellaneous sources.

Susceptibility Testing

Antibiotic disk susceptibility testing was performed according to the procedure described by the National Committee for Clinical Laboratory Standards.[15] Microorganisms were considered susceptible to Augmentin if the zone size was equal to or greater than 20 mm for *Staphylococcus* and 18 mm for all other gram-positive and gram-negative bacteria. Quality control organisms included in daily testing were *Escherichia coli* ATCC 25922, *S. aureus* ATCC 25923, and *P. aeruginosa* ATCC 27853. Mueller-Hinton agar with a pH between 7.2 and 7.4 was used in the tests. The susceptibility plates were incubated for 18 to 24 hours at 35°C.

Results

A total of 957 isolates from clinical specimens were tested in vitro by the disk diffusion test to determine the susceptibility of these bacteria to Augmentin and other routinely used antimicrobial agents. Of these bacteria, 354 (37%) were isolated from urine, 134 (14%) from the respiratory tract, 77 (8%) from the genitalia, 57 (6%) from blood, and the rest from body fluids (71), wounds (130), tissues (28), and abscesses (106). The results of susceptibility testing against facultative gram-negative bacteria are shown in Table 1. Of the 538 members the Enterobacteriaceae family tested, 410 (76%) were susceptible to Augmentin, whereas only 272 (51%) were inhibited by ampicillin.

Although the susceptibility pattern of organisms like *Citrobacter, Morganella, Sal-*

TABLE 1. *Susceptibility pattern of Enterobacteriaceae to Augmentin and other antibiotics.*

	% susceptible								
Organism (no. tested)	Augmentin	Ampicillin	Amikacin	Cephalothin	Ceftazidime	Gentamicin	Trimethoprim-sulfamethoxazole	Piperacillin	Tetracycline
Citrobacter sp. (8)	0	0	100	75	88	100	0	63	25
E. coli (309)	83	38	97	81	100	95	56	52	56
Enterobacter sp. (30)	0	0	98	23	73	78	70	63	83
K. pneumoniae (126)	88	3	98	96	100	92	84	86	50
K. oxytoca (12)	41	0	100	0	100	41	50	41	0
Morganella morganii (4)	0	0	100	0	100	100	100	100	50
P. mirabilis (21)	81	47	100	61	100	71	61	81	9
P. vulgaris (7)	66	33	100	33	100	100	100	100	66
Salmonella enteritidis (12)	93	86	–	–	–	86	100	–	73
S. typhi (4)	100	100	100	100	100	100	100	100	100
Serratia marcescens (6)	0	0	60	0	100	80	80	80	0
Shigella flexneri (5)	0	0	–	–	–	100	20	–	20

monella, and *Shigella* is reported in Table 1, the numbers of each of these isolates are too low for statistic significance. The same is true of organisms numbering less than 10 in Tables 2 and 3.

Of the pseudomonads tested, all strains of *P. aeruginosa* and *P. fluorescens* were resistant to Augmentin. However, two (28%) isolates of *P. maltophilia* and four strains of *P. putrefaciens* (100%) were inhibited by Augmentin. Ticarcillin, piperacillin, ceftazidime, and all the aminoglycosides were more effective against the *Pseudomonas* species used (Table 2).

Of the 174 strains of *S. aureus* tested, only five (3%) were susceptible to ampicillin, but 162 (93%) were susceptible to Augmentin (Table 3). Twelve of these isolates were resistant to oxacillin, and all these were the only strains that were also resistant to Augmentin. All the isolates of micrococci and enterococci were inhibited by this antibiotic. Of the other nine antibiotics tested in our laboratory against gram-positive cocci, only vancomycin was found to be superior to Augmentin.

Discussion

A wide variety of antibiotics are used to combat infectious diseases in hospitals as well as in the community. Although many of these drugs are effective against microorganisms, many have serious side effects. An ideal antibiotic is the one which is active against the infecting agent without any ill effects on the patient. The only groups of drugs that come close to the definition of ideal antibiotics are probably penicillins and cephalosporins in nonallergic hosts. Thus, penicillin is usually the drug of choice to treat infections caused by susceptible bacteria in nonallergic patients. However, many of these bacteria develop resistance to penicillin by producing beta-lactamase and thus making these drugs unsuitable

TABLE 2. *In vitro activity of antimicrobial agents against Pseudomonas and Acinetobacter.*

	% susceptible									
Bacterium (no. tested)	Augmentin	Ampicillin	Amikacin	Cephalothin	Ceftazidime	Gentamicin	Piperacillin	Trimethoprim-sulfamethoxazole	Ticarcillin	Tetracycline
P. aeruginosa (101)	0	0	86	0	95	56	93	1	81	1
P. maltophilia (7)	28	28	75	0	42	42	14	85	28	28
P. putrefaciens (4)	100	100	100	0	100	100	100	100	100	100
P. fluorescens (2)	0	0	100	0	100	100	100	0	100	0
Other *Pseudomonas* sp. (10)	20	10	70	10	80	50	70	30	40	20
A. calcoaceticus										
var. *antiratum* (6)	16	0	83	0	83	83	83	66	100	33
var. *woffi* (5)	100	80	80	20	100	40	80	80	100	80

TABLE 3. *Antimicrobial activity of Augmentin and other antibiotics against gram-positive cocci.*

	% susceptible									
Bacterium (no. tested)	Augmentin	Ampicillin	Clindamycin	Cephalothin	Erythromycin	Oxacillin	Piperacillin	Trimethoprim-sulfamethoxazole	Tetracycline	Vancomycin
S. aureus, oxacillin sensitive (164)	100	3	100	100	98	100	3	98	76	100
S. aureus, oxacillin resistant (12)	0	0	50	0	0	0	0	100	0	100
S. epidermidis (58)	62	8	62	78	56	30	8	58	70	100
Micrococci (2)	100	0	100	0	0	0	0	100	100	100
Enterococci (58)	100	92	0	2	40	0	0	87	42	100

for use. Combining clavulanic acid with amoxicillin in Augmentin overcomes this problem. Clavulanic acid by itself has weak broad-spectrum antibiotic activity that is too limited to be therapeutically useful. However, it irreversibly inactivates many plasmid-mediated beta-lactamases.[5] The cephalosporinase types of enzymes found in *P. aeruginosa, Enterobacter*, and *Serratia* organisms and the chromosomally mediated penicillinases of *E. coli* are usually not inhibited by clavulanic acid.[17] We found that none of the former three species and only 18 of the 68 (26%) ampicillin-resistant *E. coli* were inhibited by Augmentin.

Previous studies have shown that clavulanic acid not only irreversibly inactivates beta-lactamase but also exhibits synergism with amoxicillin against amoxicillin-resistant bacteria.[7,8,18,19] The rate of amoxicillin resistance in Saudi Arabia is markedly higher than those reported in the United States and Europe.[20,21] In this study we found that these same clinical strains of *E. coli, Klebsiella pneumoniae, Proteus* organisms, and staphylococci showed increased susceptibility to Augmentin as compared to ampicillin. Since these bacteria constitute a great majority of organisms that are implicated in clinical disease, Augmentin appears to be a valuable drug in their treatment.

References

1. Bell SM, Plowman D. Mechanisms of ampicillin resistance in Haemophilus influenzae from respiratory tract. Lancet 1980;1(8163):279-80.
2. Rammelkamp CH, Moxon T. Resistance of Staphylococcus aureus to the action of penicillin. Proc Soc Biol 1942;51:386.
3. Richmond MH. Beta-lactamases. Int J Clin Pharmacol Biopharm 1979;17(3):135-6.
4. Rogers HJ, Forsberg CW. Role of autolysins in the killing of bacteria by some bactericidal antibiotics. J Bacteriol 1971;108:1235-43.
5. Reading C, Cole M. Clavulanic acid: a beta-lactamase-inhibiting beta-lactam from Streptomyces clavuligerus. Antimicrob Agent Chemother 1977;11(5):852-7.
6. Goldstein FW, Kitzis MP, Malhurst C, et al. Clinical evaluation of the formulation clavulanic acid plus amoxicillin in the treatment of urinary tract infections due to beta-lactamase producing bacteria. Curr Chemother Infect Dis 1980;1:349-51.
7. Hunter PA, Coleman K, Fisher J, Taylor D. In vitro synergistic properties of clavulanic acid with ampicillin, amoxycillin, and ticarcillin. J Antimicrob Chemother 1980;6(4):455-70.
8. Van Klingeren B, Dessens-Kroon M. The influence of clavulanic acid on the susceptibility to amoxycillin of beta-lactamase producing strains of *Haemophilus influenzae* using different inoculum sizes. J Antimicrob Chemother 1979;5:322.
9. Kosmidis J, Anyfantis A, Stahakis C, et al. Augmentin (amoxycillin plus sodium clavulanate, a beta-lactamase inhibitor) is active in amoxicillin-resistant infections. Curr Chemother Infect Dis 1980;1:330-1.
10. Leigh DA, Bradnock K. Amoxicillin/clavulanic acid (Augmentin) therapy in complicated urinary tract infections. Curr Chemother Infect Dis 1980;2:332-4.
11. Perryman F, Johnson S, Qadri SM. In vitro activity of Augmentin against pathogenic bacteria and its comparison with other antibiotics. Chemotherapy 1983;29(2):111-5.
12. Glupczynski Y, McGillavry C, Yourassowski E. Comparative in vitro activity of Augmentin against community and hospital acquired gram-negative bacteria. Acta Clin Belg 1988;43:109-14.
13. Kirei BR, Mhalu FS, Pallangyo PK, Seif SAB. The efficacy of Augmentin as a beta-lactam antibiotic in surgical and medical practice. East Afr Med J 1987;64:499-504.
14. Eltahawy E, Fouad Khalaf RM. Comparative in vitro activity of amoxycillin/clavulanate (Augmentin), ceftazidime and ceftriaxone against hospital strains of gram-negative and positive bacteria. Chemiotropika 1988;7:75-9.
15. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobic disc susceptibility tests. Approved standard ASM-2. National Committee for Clinical Laboratory Standards, Villanova, 1984.
16. Lennette EH, Balows A, Hanslar WJ, Shadomy HJ. Manual of clinical microbiology. 4th ed. Washington: American Society for Microbiology, 1985.
17. Neu HC. Molecular modifications of antimicrobial agents to overcome drug resistance. Antibiot Chemother 1975;20:87-111.
18. Matsura M, Nakazawa H, Hashimoto T, Mitsuhashi S. Combined antibacterial activity of amoxicillin with clavulanic acid against ampicillin-resistant strains. Antimicrob Agent Chemother 1980;17(6):908-11.
19. Yogev R, Melick C, Kabat WJ. In vitro and in vivo synergism between amoxicillin and clavulanic acid against ampicillin-resistant Haemophilus influenzae type b. Antimicrob Agent Chemother 1981;19(6):993-6.
20. Qadri SM, Ostrawski S, Johnson S, Flournoy DJ. Differences in antimicrobial susceptibilities of clinical isolates in Saudi Arabia and the United States. J Natl Med Assoc 1987;79(4):433-7.
21. Qadri SM, Rizvi WH, Rahman SA, Flournoy DJ. Antimicrobial resistance of *Escherichia, Klebsiella* and *Pseudomonas* in Saudi Arabia and U.S.A. J Natl Med Assoc (in press).

FINE-NEEDLE ASPIRATION IN DIAGNOSIS OF CUTANEOUS LEISHMANIASIS

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قارنا خزعة الارتشاف بالإبرة الرفيعة لآفات الجلد عند الاشتباه بالليشمانيات مع لطاخات السحج واللمس لهذه الآفات. وقد امتازت خزعة الارتشاف بالإبرة الرفيعة لأنها كانت أسرع وأقل إيلاما وأنتجت عينات ذات نوعية أفضل. هذا بالإضافة إلى أن النتائج السلبية الكاذبة كانت أقل.

We have compared fine-needle aspiration biopsy (FNAB) of the skin lesions of suspected cutaneous leishmaniasis with scraping and touch smears of those lesions. The FNAB technique was shown superior because it was less painful and faster and provided better quality of material. In addition, it gave less false-negative results.

Since the reintroduction of fine-needle aspiration biopsy (FNAB) a few years ago,[1] after Martin and Ellis first described the technique,[2] the procedure has been widely accepted as a rapid diagnostic tool not only in the case of tumors, but also for the diagnosis of pulmonary opportunistic infections,[3] and other lesions.

All clinical forms of leishmaniasis are caused by a wide variety of parasitic protozoa within the genus *Leishmania*, transmitted by the bite of sandflies, usually *Phlebotomus* sp. in the Eastern hemisphere and *Lutzomyia* sp. in the Western hemisphere.[4]

In the tissue, the tiny (less than 3 fL), nonflagellated organism is in the leishmanial amastigote form and multiplies within histiocytes.

The species of *Leishmania* causing leishmaniasis are morphologically identical. The leishmanial amastigotes are ovoid or round with a thin cell membrane and a relatively large nucleus and a rod-shaped kinetoplast.[5]

Cutaneous leishmaniasis includes three distinct clinical entities: tropical sores, mucocutaneous leishmaniasis, and disseminated cutaneous leishmaniasis. Diagnosis of the lesion is easily accomplished by demonstrating the *Leishmania* organisms in smears, biopsy specimens, cultures in special biphasic medium, or by monoclonal antibody techniques.[6]

Cutaneous leishmaniasis is found frequently in Saudi Arabia. Reported cases in the Riyadh area have increased from 92 in 1978 to 2364 in 1985.[7]

Every year about 300 cases are referred to the histopathology department of the Central Laboratory with the clinical diagnosis of cutaneous leishmaniasis (Figure 1).

Routinely, we have been using scraping and touch preparation from these lesions to prepare smears, which have been stained with a Giemsa stain and screened for *Leishmania* organisms.

Although the results are fairly satisfactory, the procedure is painful to the patient, and the smears are not satisfactorily clean which makes screening more difficult and may leave a rough surface on the lesion which potentially exposes it for secondary infection. The rate of positive results has been less than expected.

Because of these factors, we decided to try FNAB and compare both methodologies.

Materials and Methods

A 20-mL plastic syringe with a 22-gauge needle was used for FNAB. After initial cleaning with

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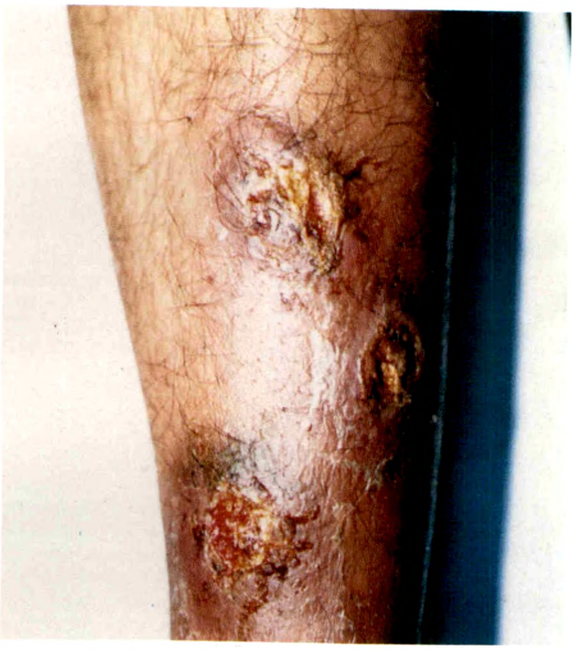

FIGURE 1. Cutaneous leishmaniasis with multiple chronic ulceration of the skin.

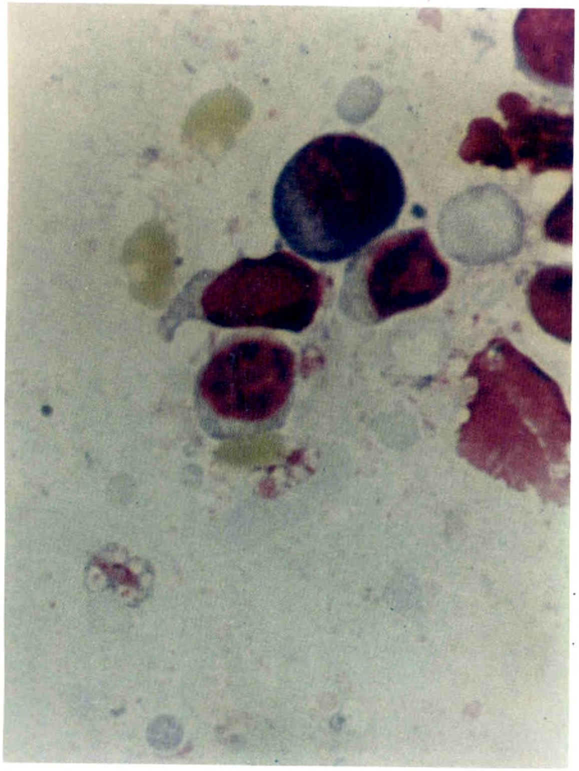

FIGURE 2. Positive smear showing amastigotes by FNAB technique from the patient shown in Figure 1. The background is clean, and the characteristics of *Leishmania* organisms are easy to identify.

70% alcohol antiseptic, the lesion edge was entered with a needle directed toward the center horizontally, avoiding deep penetration. The needle was totally rotated to loosen the tissue, and suction was gently applied. The needle was then moved in several directions within the lesion, and at each location, gentle suction was applied to draw more material. The aspirated material in the needle was transferred to a clean glass slide. Smears were prepared immediately. These were stained with a Giemsa stain and screened for amastigotes, recognized by their size, shape, and staining characteristics, and especially by the presence of the intracytoplasmic kinetoplast (Figure 2).

Touch smears were also prepared from the same lesion by means of the scraping procedure. After the usual cleaning, a sharp sterilized blade was used to scrape the margin of the lesion until enough oozing serum was obtained, which usually takes about 5 minutes.

The smears from both methods were compared independently by a group of four histopathologists who had agreed on the methods, and the methods were strictly adhered to.

A smear was considered positive when a typical leishmanial amastigote was identified under oil immersion magnification, free in the smear, or within the histiocytes. Each positive finding was confirmed by at least two of the four histopathologists.

Each negative slide was examined for at least 5 minutes by the four pathologists before it was considered negative for *Leishmania* organism.

Scoring system was used only for evaluation of quality of the material and smears but not for the number or organism observed.

The smears were considered adequate when they were free of any significant amount of bacteria, tissue strands/fibers, cellular debris, and blood. When any one or more of these factors was present in an amount great enough to interfere with proper evaluation, the smears were considered inadequate (Table 1). No bacteriologic culture for *Leishmania* species or biopsy of the specimens was done.

Results and Comments

The procedures were done in 50 patients with

TABLE 1. *Quality of smear preparation..*

Procedure	Adequate	Inadequate	Total
FNAB	48	2	50
Scraping	42	8	50
Total	90	10	100

TABLE 2. *Presence of amastigote in smear preparation.*

Procedure	Positive	Negative	Total
FNAB	30	20	50
Scraping	24	26	50
Total	54	46	100

the clinical diagnosis of cutaneous leishmaniasis. As can be seen in Table 2, in 60% of the cases of clinically diagnosed cutaneous leishmaniasis, leishmanial amastigotes were demonstrated in the smears taken by the FNAB compared with 48% using the scraping procedure, resulting in less false-negative results (12.0%) with FNAB.

This small discrepancy probably is due to the better quality of smears obtained with the FNAB technique, since 96% (48/50) of the smears obtained with this procedure were considered adequate (Table 1), with less cellular debris and bacteria. Therefore, identification of *Leishmania* organisms was easier using the FNAB technique compared with the 84% (42/50) positive diagnoses obtained from the scraping procedure (Figure 2).

Besides better results in the identification of the parasites, we observed that the FNAB procedure is faster and less painful to the patient. We have been using the FNAB technique on all patients for 1 year.

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References

1. Frable WJ. Fine-needle aspiration biopsy: a review. Hum Pathol 1983;14(1):9-28.
2. Martin HE, Ellis EB. Biopsy by needle puncture and aspiration. Ann Surg 1930;92:169-81.
3. Bhatt ON, Miller R, Le Riche J, King EG. Aspiration biopsy in pulmonary opportunistic infections. Acta Cytol 1977;21(2):206-9.
4. Peters W, Al-Zahrani MA. The leishmaniases: a public health problem in Saudi Arabia. Saudi Med J 1987;8(4):333-43.
5. Robbins SL. Pathologic basis of disease. 3rd ed. Philadelphia: WB Saunders, 1984:371.
6. Marinkelle CJ. Recent advances in leishmaniases. Ann Saudi Med 1987;7(2):93-103.
7. Connor DG, Neafia RC. Cutaneous leishmaniasis. In: Binford CH, Connor DH, eds. Pathology of tropical and extraordinary diseases. Washington DC: Armed Forces Institute of Pathology, 1976;258.

THYROTOXICOSIS: EXPERIENCE FROM THE KING KHALID UNIVERSITY HOSPITAL, RIYADH

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شوهد واحد وتسعون مريضا بالتسمم الدرقي، (٥٧ أنثى و٣٤ ذكرا، ٥٢ سعوديا و٣٩ من غير السعوديين)، في مستشفى الملك خالد الجامعي بالرياض. كان متوسط أعمارهم ٣١,٨ سنة، وكان ثمانية وسبعون منهم مصابين بمرض جريفز، ولم تشاهد حالات تسمم درقي سببها التهاب الدرقية الصامت. كان رجحان نسبة إصابة الإناث منخفضا لدى السعوديات، نسبة الإناث إلى الذكور (١,٧ : ١) مقارنة بنسبة رجحان أعلى (٣,٥ : ١) في مجموعة غير السعوديين. وغياب الوذمة المخاطية أمام الظنبوب. كان العلاج الطبي هو الأسلوب المتبع مع جميع المرضى في بادىء الأمر والعلاج الصياني لستين مريضا. وأجري استئصال جُلّ الدرقية لثلاثة وعشرين مريضا، كما عولج ثمانية مرضى باليود المشع.

Ninety-one patients with thyrotoxicosis, 57 females and 34 males, 52 Saudis and 39 non-Saudis, were seen at King Khalid University Hospital, Riyadh. The mean age was 31.8 years. Seventy-eight patients had Graves' disease. Thyrotoxicosis caused by silent thyroiditis was not observed. Thyrotoxicosis had a low female preponderance with a female-to-male ratio of 1.7:1 in the Saudi patients and 3.5:1 in non-Saudis. Patients with Graves' disease were characterized by a lower rate of ophthalmopathy (30%) than previously reported and by absence of pretibial myxedema. Medical treatment was the initial mode of management in all patients and in 60 patients was the maintenance treatment. Subtotal thyroidectomy was performed in 23 patients, and radioactive iodine ablation was the treatment for eight patients.

Although thyrotoxicosis has worldwide distribution, its prevalence in different parts of the world is variable. For example, it has traditionally been reported to be much less common in Africa than in countries of Europe and North America.[1-3] Saudi Arabia is a country that has seen very dramatic changes in its socioeconomic status over the last 25 years. This may be important since thyrotoxicosis was once considered as one of the "diseases of Western civilization."[4] This article describes the clinical manifestations of thyrotoxicosis in this part of the world and discusses different modes of treatment.

Patients and Methods

The present study was a retrospective analysis of cases of thyrotoxicosis seen at King Khalid University Hospital (KKUH), Riyadh, over a period of 4 years from 1983.

Patients seen at this hospital include Saudis as well as patients of other nationalities, mainly from neighboring Asian and African countries. All patients were subjected to a full history and physical examination, including a detailed examination of the thyroid. Patients seen in our hospital with thyrotoxicosis routinely have thyroid scan using radioactive iodine 123 (^{123}I). Thyroid function tests (T3, T4, TSH) were done by the radioimmunoassay method using commercial kits. Antimicrosomal and antithyroglobulin antibodies were measured using the hemagglutination technique.

The different causes of thyrotoxicosis were

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diagnosed based on the typical physical findings and thyroid scan abnormalities.

Results

Ninety-one patients with thyrotoxicosis were seen, 57 females (63%) and 34 males (37%). Of the 91 patients, 52 were Saudi and 39 were non-Saudi. The mean age was 31.8 years. The female-to-male ratio was 1.7:1 in the Saudi patients and 3.5:1 in the non-Saudis.

The diagnosis of Graves' disease was made on the basis of hyperthyroidism, diffuse goiter with or without ocular signs, and raised ^{123}I uptake. The diagnosis of toxic nodular goiter was made on the basis of hyperthyroidism and the topographical examination of the thyroid together with the appearance of ^{123}I thyroid scan. Of the 91 patients, 78 (85.7%) had Graves' disease, six (6.6%) had toxic multinodular goiter, and in two patients (2.2%), the diagnosis was toxic adenoma. In five patients (5.5%) the exact etiology was not obvious from the studies available, as the work-up of these patients was incomplete. In patients with toxic multinodular goiter there was no history of exposure to an iodine-containing compound. Table 1 shows the incidence of symptoms and signs in the patients studied.

The mean T4 ± SD was 254 ± 22.5 nmol/L (reference interval, 54 to 142 nmol/L), and the mean T3 ± SD was 6.45 ± 0.88 nmol/L (reference interval, 0.8 to 2.46 nmol/L). Eighty-seven patients had elevations of both T3 and T4, and four had pure T4 toxicosis. There were no cases of pure T3 toxicosis. Of 42 patients in whom microsomal and thyroglobulin antibody titers were determined, 16 (38.1%) had positive antimicrosomal antibody titers of more than 1/1600 and four (9.5%) had antithyroglobulin antibody titers of more than 1/1600 (Table 2).

All patients were initially treated medically, usually with carbimazole or propylthiouracil (4% of cases) with or without a beta-blocker. The initial daily doses for carbimazole and propylthiouracil were 30 to 45 mg and 300 to 450 mg in divided doses, respectively. Daily maintenance doses were 10 to 15 mg for carbimazole and 100 to 150 mg for propylthiouracil. Surgery was the treatment of choice in 23 patients (25%). Many of the patients were referred to surgeons because of big goiter and pressure symptoms. After 1 year of postoperative follow-up, none of these patients had had clinical or biochemical relapse. Hypoparathyroidism and recurrent laryngeal nerve palsy were not observed postoperatively.

TABLE 1. *Incidence of symptoms and signs of 91 patients with thyrotoxicosis.*

Symptom	No. (%)	Sign	No. (%)
Palpitations	73 (80.2)	Goiter	
Heat intolerance	57 (62.6)	diffuse	69 (75.8)
		nodular	5 (5.5)
Increased sweating	57 (62.6)	Tachycardia	73 (80.2)
Fatigue	55 (60.4)	Tremor	51 (56.0)
Weight loss	50 (54.9)	Exophthalmos	
Increased appetite	45 (49.5)	bilateral	24 (26.4)
Tremor	41 (45.0)	unilateral	4 (4.4)
Nervousness	31 (34.1)	Bruit over goiter	21 (23.1)
Dyspnea	31 (34.1)	Lymphadenopathy	9 (9.9)
Thyroid swelling	30 (33.0)	Splenomegaly	5 (5.5)
Eye complaints	18 (19.8)	Atrial fibrillation	4 (4.4)
		Vitiligo	2 (2.2)

TABLE 2. *Radionuclide, biochemical, and immunologic parameters of thyrotoxic patients seen at King Khalid University Hospital, Riyadh.*

	No. patients (%)
Group A (91 patients)	
Radioisotope study using ^{123}I	
Diffuse increased uptake	78 (85.7)
Toxic nodular	6 (6.6)
Toxic adenoma	2 (2.2)
Not done	5 (5.5)
Biochemical features	
Both T3 and T4 elevated*	87 (95.6)
Only T4 elevated	4 (4.4)
Only T3 elevated	0
Group B (42 patients)	
Antithyroid antibody status (N = 20)	
Antimicrosomal antibody titer, 1/1600	16 (38.1)
Antithyroid antibody titer, 1/1600	4 (9.5)

* T3 reference interval, 0.8 to 2.46 nmol/L; mean ± SD, 6.45 ± 0.88 nmol/L. T4 reference interval, 54 to 142 nmol/L; mean ± SD, 254 ± 22.5 nmol/L.

N.B.: Group A contains all patients (N = 91) diagnosed with thyrotoxicosis. Group B is a subset of 42 patients who underwent microsomal and thyroglobulin antibody titer determination.

Hypothyroidism was diagnosed in three of the 23 patients during a 12-month follow-up period. Radioactive iodine ablation (7 to 10 mCi) was used for only eight patients, none of them below the age of 30 years. Hypothyroidism developed in five of them in the first year after treatment. Medical treatment was maintained for a mean of 16 months for the rest of the patients (60 patients). These patients were evaluated every 2 to 3 months. Of those 60 patients, 12 were lost to follow-up after they had been rendered euthyroid medically. The recurrence rate of thyrotoxicosis in the remaining group (48 patients) after stopping their medical treatment was 54%.

Discussion

This is a descriptive study of thyrotoxicosis in Saudi Arabia which aims to examine if there are any geographical variations in the pattern of the disease, its etiology, and its manifestations.

Although we do not know much about its prevalence, the first observation to be made is that thyrotoxicosis is not a rare disease in this country. Whether a change in dietary iodine intake has followed the socioeconomic changes in Saudi Arabia and which may have caused the appearance of thyrotoxicosis (jodbasedow phenomenon or iodine-induced hyperthyroidism) in individuals with previous goiters is worth considering, although Saudi Arabia is not known as an endemic goiter region. Similar observations were made in Tasmania and in Britain.[5,6]

The finding of a marginal female preponderance in this study is striking and probably the lowest quoted in the world literature.[7-9] This confirms the observation noted by Johansen et al.[10]

Of the causes of thyrotoxicosis, Graves' disease was found to be the commonest. The incidence of ophthalmopathy was lower than in other series.[11,12] Also, pretibial myxedema and thyroid acropachy were not observed in any of our patients, including those with ophthalmopathy.

Despite the recent interest in silent thyroiditis (lymphocytic thyroiditis) as an important and common cause of thyrotoxicosis, amounting to 15% to 20% in some series, this was not the case in our study.[13,14] However, the incidence of silent thyroiditis has been variable geographically.[15]

In terms of management, treatment was the initial treatment in all the patients. Facilities for radioactive iodine treatment are becoming more widely available in this country. Considering the high rate of patients lost to follow-up while on treatment in our study, radioactive iodine ablation and early thyroxine replacement should be the treatment of choice for patients above 30 years of age. However, it may have to be considered for the younger noncompliant patients as well, as its use in this young age group was found to be equally safe and effective.

References

1. Davey WW, Ogunlesi TO. Thyrotoxicosis in Nigeria. W Afr Med J 1963;12:174-80.
2. Cardozo LJ, Viegas OA. Thyrotoxicosis in Ugandan Africans. Trans R Soc Trop Med Hyg 1975;69(2):201-4.
3. Gitau W. An analysis of thyroid disease at the Kenyatta National Hospital. East Afr Med J 1975;52(10):564-70.
4. Towell HC. Western diseases, Western diets, and fibre. East Afr Med J 1978;55(6):283-9.
5. Stewart JC. Epidemiology and pathogenesis of iodine-induced thyrotoxicosis in Northern Tasmania. NZ Med J 1975;81(531):25-6.
6. Barker DJ, Phillips DI. Current incidence of thyrotoxicosis and past prevalence of goitre in 12 British towns. Lancet 1984;2(8402):567-70.
7. Mogensen EF, Green A. The epidemiology of thyrotoxicosis in Denmark: incidence and geographical variation in the Funen region, 1972-1974. Acta Med Scand 1980;208(3):183-6.
8. Abdulkadir J, Besrat A, Abraham G, Gebre T. Thyrotoxicosis in Ethiopian patients—a prospective study. Trans R Soc Trop Med Hyg 1982;76(4):500-2.
9. Haraldsson A, Gudmundsson ST, Larusson G, et al. Thyrotoxicosis in Iceland 1980-1982: an epidemiological survey. Acta Med Scand 1985;217(3):253-8.
10. Johansen K, Khan M, Woodhouse NJY. High-dose iodine 131 treatment of hyperthyroidism: experience at King Faisal Specialist Hospital and Research Centre. Ann Saudi Med 1988;8(6):466-9.
11. Crooks J, Murray IPC, Wayne EJ. Statistical methods applied to the clinical diagnosis of thyrotoxicosis. Q J Med 1959;28:211-34.
12. Oddie TH, Boyd CM, Fisher DA, et al. Incidence of signs and symptoms in thyroid disease. Med J Aust 1972;2:981-6.
13. Dorfman SG, Cooperman MT, Nelson RL, et al. Painless thyroiditis and transient hyperthyroidism without goiter. Ann Intern Med 1977;86(1):24-8.
14. Woolf PD. Transient painless thyroiditis with hyperthyroidism: a variant of lymphocytic thyroiditis? Endocrin Rev 1980;14(4):411-20.
15. Strakosch CR. Thyroiditis. Aust NZ J Med 1986;16(1):91-100.

HEMOGLOBIN LEVELS AND BLOOD GROUPS IN PERSONS LIVING AT A HIGH ALTITUDE

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أجريت دراسة لتحديد مستويات خضاب الدم وزمر الدم لدى قاطني المرتفعات (٢٥٠٠ إلى ٣٠٠٠ متر فوق سطح البحر). تم الحصول على مستويات الخضاب وزمر الدم من الأصحاء المتقدمين لفتح ملفات صحية في مركز الرعاية الأولية. قدر مستوى الخضاب بطريقة "CYANMETHEMOGLOBIN" واستخدام نظام ABO في تحديد زمر الدم. أظهرت نتائج الدراسة زيادة مستوى الخضاب لدى الذكور عنه لدى الإناث منذ سن ١٥ عاما. وتراوح متوسط القيمة لدى الذكور من سن الطفولة إلى سن متقدمة بين ١٣٠ و ١٦٣ غرام/لتر ولدى الإناث بين ١٢٨ و ١٥٠ غرام/لتر. كان توزيع زمر الدم لدى المجموعة ككل كما يلي: ٣٣٪ A ، ١٢٪ B ، ٥٢٪ O ، وحوالي ٣٪ AB كان العامل الريصي سلبيا لدى ٤,٨٪. ولم يكن لمستوى الخضاب علاقة بزمر الدم. قد تفيد هذه النتائج الأطباء في تقييم حالات فقر الدم لدى قاطني المرتفعات أو الإداريين المسؤولين عن تأمين زمر معينة من الدم للمستشفيات.

A study has been conducted to determine the hemoglobin norms and blood groups of the people living at a high altitude (2500 to 3000 meters above sea level). Hemoglobin levels and blood groups were obtained from healthy individuals coming for family registration with the primary health center. Hemoglobin was estimated by the cyanmethemoglobin method, and the ABO grouping system was used. Results showed that males had higher hemoglobin levels than females from the age of 15 years. From childhood to old age the mean value for males ranged from 130 to 163 g/L and for females from 128 to 150 g/L. In all, 33% had group A, 12% group B, 52% group O, and nearly 3% group AB. Only 8.4% had Rh-negative blood. Blood groups had no relation to hemoglobin levels. These findings may help physicians assess anemia in patients living at high altitudes and administrators responsible for procurement of specific blood groups for hospitals.

A person is considered anemic when his or her hemoglobin level falls below two standard deviations from the mean for a normal population (140 g/L for men, 120 g/L for women) at sea level.[1] Physicians usually refer to hemoglobin levels more frequently than other hematologic characteristics for patient care. To determine hemoglobin reference values of the Saudi population, studies have been done by Sebai,[2] Hassan et al,[3] and others. A large fraction of the Saudi population lives at high altitudes. Their hemoglobin levels for assessing them as anemic or normal have not been determined adequately. A study done by Scott[4] was with a small group of male subjects and the altitude of the place was 745 meters; the levels obtained in this study can not be used for comparison with all ages and sexes. The study done by Bacchus et al was at 1000-meter altitude.[5] Many southern region people, however, live at an altitude higher than 1000 meters. Whether blood group has any influence on hemoglobin level at a higher altitude is now known. In addition, although blood groups A and O are said to be

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most prevalent in Saudis,[2] studies taking a sufficient number of samples have not been done. This is essential in procuring specific types of blood from abroad for hospital emergencies. We, therefore, wanted to examine these issues anew in a healthy population living at an altitude of 2500 to 3000 meters above sea level in Abha, Saudi Arabia.

Materials and Methods

The study was done in Abha City, which is situated at an altitude of 2500 to 3000 meters above sea level. The population is composed of Saudis, Egyptians, Yemenis, and other nationalities. Of the three primary health care centers in Abha, Shamasan Centre provides primary care for about 30% of the city's population. To avail themselves of health care facilities, families must register with the primary health care center. All members of the family are to present themselves for a health check-up and for laboratory investigations of stool, blood, and urine. The nurses of the center informed as many families as possible by visiting them to encourage and remind them to attend the center on particular dates for health check-up and registration. Family members were also reminded of appointments by telephone. They were examined by a physician and a dentist. Laboratory investigations were done by a medical technologist, and then a family file was opened for them. All ailments, treatment, outcome of illness, results of investigations, and pregnancies were recorded in the family file.

We obtained the initially determined hemoglobin levels and the blood groups of all the family members examined. The investigations included all ages and both sexes. Incomplete reports and results of investigations on pregnant women were excluded.

For estimation of hemoglobin levels the cyanmethemoglobin method has been used.[6] For grouping, ABO blood grouping has been followed.[7] For measuring the validity of differences, the simple chi-square test was applied.[8]

Results

Table 1 shows the distribution of hemoglobin levels of 1604 persons by age and sex.

Of the male population, 29.9% had a hemoglobin level of 121 to 140 g/L; 35.4%, 141 to 160 g/L; and 28.3%, 161 to 180 g/L.

In the female group, 43.4% had a hemoglobin level of 121 to 140 g/L; 39.7%, 141 to 160 g/L; and 6.7%, between 161 and 180 g/L.

The differences in prevalence rates of hemoglobin levels of 121 to 140 g/L and 161 to 180 g/L between males and females were statistically significant. There was none with Hb level over 180 g/L.

TABLE 1. *Levels of hemoglobin by age, sex, and percentage of population.*

	Male Hb (g/L)						Female Hb (g/L)					
Age (y)	≤100	101–120	121–140	141–160	161–180	Mean	≤100	101–120	121–140	141–160	161–180	Mean
0–4	1.6	18.5	58.1	21.0	0.8	130	0.9	23.9	60.7	13.7	0.9	128
5–9	–	10.2	49.7	35.9	4.1	137	–	9.3	56.7	32.0	2.0	135
10–14	0.8	0.8	36.3	54.0	8.1	144	0.8	6.8	43.2	44.7	4.5	139
15–19	–	1.9	7.5	47.2	43.4	156	–	8.9	35.4	46.8	8.9	141
20–29	–	1.9	3.8	25.0	69.2	162	1.4	7.6	39.6	45.1	6.3	139
30–39	–	–	9.8	24.4	65.9	161	0.9	6.0	38.5	47.0	7.7	141
40–49	–	–	1.1	34.5	64.4	163	–	6.5	23.9	50.0	19.6	147
50–59	–	–	–	40.0	60.0	162	–	–	14.3	71.4	14.3	150
60 +	–	–	–	42.1	57.9	162	–	40.0	24.0	40.0	32.0	150
Total %	0.4	6.0	29.9	35.4	28.3	147	0.6	9.5	43.4	39.7	6.7	138
No. of subjects	3	46	229*	271	217†	766	5	80	364*	333	56†	838

* The difference in prevalence rate of 121 to 140 g/L hemoglobin level between male and female subjects is significant ($P < 0.01$).
† The difference in prevalence rate of 161 to 180 g/L hemoglobin level between male and female subjects is significant ($P < 0.001$).

In both males and females, adults had higher hemoglobin levels than children up to 14 years old. Male children up to 14 years old had higher hemoglobin levels than female children of the same age group. Of the male children 10 to 14 years old, 36.3% had moderately low hemoglobin levels (121 to 140 g/L), while 43.2% of the female children had the same hemoglobin level. Of male children of the same group, 54.0% had medium hemoglobin level (141 to 160 g/L), and 45% of the female children had such levels. In the age group 15 to 19 years, 90.6% of the males had a hemoglobin level equal or over 140 g/L, while only 55.7% of females had such a level. Overall, 28.3% of males and 6.7% of females had high hemoglobin levels (161 to 180 g/L).

Figure 1 shows the 50th percentile distribution of hemoglobin levels (rounded to the nearest whole number) for male and female subjects by age. The 50th percentile level for all children, both male and female up to 9 years old, was 130 g/L. It was the same (130 g/L) for females between 10 and 14 years old. From the age of 15 years upward, the 50th percentile hemoglobin level for females was 150 g/L and for males 170 g/L. This 50th percentile value was up to 14 g/L more than the mean hemoglobin levels in males of all ages. In females these differences were less apparent. The differences in prevalence of 50th percentile levels between males and females from the age of 10 years were all significant statistically.

Of the 1796 people for whom hemoglobin levels and blood groups were determined, 851 were male and 945 female (Table 2). Thirty-three percent of the subjects had group A (A+ and A−), 12.2% group B (B+ and B−), 51.9% group O (O+ and O−), and 2.8% group AB (AB+ and AB−). Both A+ and B+ were more common in females than in males. Distribution of group O was almost identical in males and females. Group AB (A+) was commoner in males than in females. Of the total samples, 8.4% were Rh negative. There were no consistent associations between blood groups and hemoglobin levels.

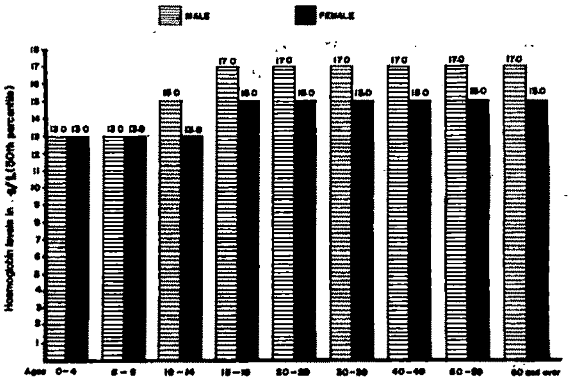

FIGURE 1. Distribution of 50th percentile hemoglobin levels by age and sex.

The blood groups by nationality are shown in Table 3. Of the 1093 persons whose precise nationality was obtained, 760 (69.5%) were Saudi, 83 (7.6%) Yemeni, 91 (8.3%) Egyptian and 159 (14.5%) were other nationalities. Of the Saudis, 30.2% had blood group A, 9.2% B, 57.1% O, and 3.6% AB. Yemenis were similar to

TABLE 2. *Levels of hemoglobin by blood groups, sex, and percentage of population.*

	Male Hb (g/L)						Female Hb (g/L)						Overall
Age (y)	≦100	101–120	121–140	141–160	161–180	Mean	≦100	101–120	121–140	141–160	161–180	Mean	prevalence rate
A+	0.4	3.8	35.1	33.9	26.8	147	0.3	9.5	43.8	39.5	6.9	139	30.2
A–	–	8.7	34.8	34.8	21.7	144	–	14.3	32.1	46.4	7.1	139	2.8
B+	–	6.2	23.7	41.2	28.4	149	1.9	6.5	42.1	36.4	13.1	140	11.4
B–	–	–	18.2	27.3	54.5	157	–	25.0	–	75.0	–	140	0.8
O+	1.0	6.1	30.7	33.8	28.7	147	0.9	9.8	44.4	38.8	6.1	138	47.4
O–	–	2.7	28.2	43.6	25.6	148	–	2.4	53.7	43.9	–	138	4.5
AB+	–	7.1	10.7	57.1	25.0	150	–	17.6	52.9	23.5	5.9	134	2.5
AB–	–	–	33.3	–	66.6	157	–	–	66.6	33.3	–	136	0.3
Total %	0.6	5.3	30.3	35.7	28.1	147	0.7	9.3	44.0	39.0	6.9	138	100.0
No. of subjects	5	45	258	304	239	851	7	88	416	369	65	945	1796

TABLE 3. *Blood groups by nationalities living in Abha City.*

Nationality		A+	A–	B+	B–	O+	O–	AB+	AB–	Total
Saudi*	No.	211	18	64	6	413	21	21	6	760
	%	27.8	2.4	8.4	0.8	54.3	2.8	2.8	0.8	69.5
Yemeni	No.	26	3	9	1	36	6	2	–	83
	%	31.3	3.6	10.8	1.2	43.4	7.2	2.4	–	7.6
Egyptian†	No.	45	–	12	2	23	3	6	–	91
	%	49.5	–	13.2	2.2	25.3	3.3	6.6	–	8.3
Others	No.	50	9	28	1	59	8	4	–	159
	%	31.4	5.7	17.6	0.6	37.1	5.0	2.5	–	14.5
Total	No.	332	30	113	10	531	38	33	6	1093
	%	30.4	2.7	10.3	0.9	48.6	3.5	3.0	0.5	99.9

* Prevalence of group O in Saudis is statistically higher ($P < 0.01$) than in the other nationalities in the area.

† Prevalence of group A in Egyptians is statistically higher ($P < 0.01$) than in the other nationalities in the area.

Saudis. Group B was more common in other nationalities than Saudis, Yemenis, and Egyptians ($P < 0.05$). Nearly 50% of the Egyptians had group A (all A+), and they had the lowest prevalence of O group.

Discussion

For patient care a clear conception about the hemoglobin levels at different heights of a country is essential for every physician. Although there are European and North American standards shown in textbooks, no Arabian standard of reference has been established by taking into consideration the 50th percentile hemoglobin level of the well-born, well-nourished, disease-free, high socioeconomic groups and using proper statistical stringency. This is not an easy task. Until an Arabian standard is available, the various levels so far reported may be used only in the areas from which the data were compiled. For the highlanders, the 50th percentile values, by age and sex, obtained in this study may be accepted as a standard for the people living at about this altitude. Our values are, however, lower than the suggested hemoglobin levels (150 to 220 g/L) at about 8000 feet above sea level.[9] Our findings are not much different from Al-Kharj (1000-meter altitude) values (155 g/L for males and 135 g/L for females) but are rather higher than the value reported by El-Hazmi et al.[10] In addition to altitude, these differences may also be partly due to nutrients, environmental factors, and methodologies of estimation. Furthermore, the previous studies were not done at the same height from the sea level. This study also confirms that the differences in hemoglobin levels obtained elsewhere, between males and females of different age groups, are also prevalent at the Abha elevation (2500 to 3000 meters above sea level). Our value is higher by approximately 19 g/L for both males and females than the values at sea level. We may consider that this difference is due to the compensatory effect of hypoxia at Abha. Further, we expected that people of certain blood groups might have some differences in hemoglobin levels, but blood groups showed no consistent association with hemoglobin levels.

The prevalence of blood groups in different nationalities is interesting. Although some studies have suggested higher and identical prevalence of A and O groups in Saudis, our study shows that only 30.2% of the Saudis of this area have group A and 57.1% group O. The Egyptians had the highest prevalence of group A (49.5%) and lowest of group O compared to others. The Egyptians and Saudis had lower rates (5.5% and 6.7%, respectively) of Rh-negative blood than the Yemenis (12.0%) and others (11.3%). Furthermore, Egyptians have no Rh-negative A or AB blood groups. This may be a characteristic of Egyptians. These variations may, however, be due to genetic influence.

We hope the information obtained in this study will be useful to physicians for patient care at high altitudes and to local administrators who are responsible for procurement of blood from abroad for hospital use.

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References

1. West JB, ed. Best and Taylor's physiological basis of medical practice. 11th ed. Baltimore: Williams & Wilkins, 1985;407-8.
2. Sebai ZA. Health in Saudi Arabia. Riyadh: Tihama Publication, 1985;1:56-94.
3. Ghafouri HM, Al-Fares AM, Islam SI, et al. Hematological reference values assessed from birth to adolescence in Saudi subjects in the area of Jeddah. Saudi Med J 1987;8(6):575-82.
4. Scott TG. A pilot study of the reference values for commoner haemotological and biochemical parameters in Saudi nationals. J Clin Pathol 1982;35(1):69-73.
5. Bacchus R, Garn[illegible]E, Madkour MM, et al. The hematology reference range for Saudi Arabians. Saudi Med J 1986;8(1):46-52.
6. Estimation of haemoglobin by cyanmethaemoglobin method. In: Dacie JV, Lewis SM, eds. Practical haematology. 5th ed. London: Churchill Livingstone, 1975:32-4.
7. ABO blood grouping: tile technique. In: Dacie JV, Lewis SM, eds. Practical haematology. 5th ed. London: Churchill Livingstone, 1975;528:532-5.
8. The chi-square test. In: Maxwell AE, ed. Analyzing qualitative data. London: Mathuen and Co, 1971:11-37.
9. Guyton AC, ed. Textbook of medical physiology. Philadelphia: WB Saunders, 1986;528-31.
10. El-Hazmi MAF, Al-Faleh FZ, Al-Mofleh AS, et al. Establishment of normal "reference" for haematological parameters for healthy Saudi Arabs. Trop Geogr Med 1982;34(4):333-9.

ANTI-DELTA-VIRUS ANTIBODY IN SERA POSITIVE FOR HEPATITIS B SURFACE ANTIGEN IN MALE SAUDI BLOOD DONORS

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أجريت مقايسة مناعية شعاعية للضد النوعي لحمة (دلتا) لدى ٤٩٠ متبرعا بالدم من الذكور السعوديين الأصحاء الذين كانت أمصالهم إيجابية لمستضد التهاب الكبد ب السطحي، وتبين وجود ضد الحمة (دلتا) في ما نسبته ١١,٢٪ (٥٥/٤٩٠) من أمصال المتبرعين. وهذه النسبة أعلى بدرجة ملموسة من نسب الوقوع المنشورة والبالغة ٣,٨٪ و٠,٥٪، و٥٪ للولايات المتحدة وكندا وإيطاليا و٨٪ و٦,٧٪ و٥,٤٪ للملكة العربية السعودية وذلك في أمصال متبرعي الدم الأصحاء حاملي إيجابية المستضد السطحي لالتهاب الكبد ب.

Anti-delta-virus antibody was determined by radioimmunoassay technique in 490 healthy male Saudi blood donors with serum positive for hepatitis B surface antigen. The presence of anti-delta-virus antibody was demonstrated in 11.2% (55/490) of donor sera. This is considerably higher than the reported incidence of 3.8%, 0.5%, and 5% from the United States, Canada, and Italy, and 8%, 6.7%, and 5.4% from Saudi Arabia in healthy HBsAg-positive blood donor sera.

The delta antigen was first described in the hepatocyte nuclei of a patient with chronic hepatitis B virus (HBV) infection by Rizzetto in 1977.[1] The antigen was initially thought to be a protein of HBV, but following transmission experiments in chimpanzees, it soon became apparent that it was the internal component of a new infectious agent, the delta virus.[2] The delta virus is a unique RNA virus, 35 to 37 nm in diameter, encapsulated by a hepatitis B surface antigen (HBsAg) coat, which replicates only in subjects with HBV infection.[3] The genome of hepatitis delta virus (1.75 kilobase of RNA) is smaller than any known RNA animal virus. The delta virus is present in most areas of the world,[4] but it is endemic in Mediterranean countries, the Middle East, Africa, and South America. In Northern Europe, the United States, and Australia, the infection is confined to users of parenteral drugs and commercial factor VIII or factor IX concentrate.[5-9] Currently, it is rare among homosexual, Chinese, and Japanese chronic carriers of HBV.

The present study was undertaken to detect the prevalence of hepatitis delta virus infection in healthy male Saudi blood donor carriers of HBV in the Central Province of Saudi Arabia.

Methods

Volunteer first-time donors were Saudi nationals from the Central Province, donating on behalf of relatives or friends.

All sera from the donated blood units were tested for HBsAg using commercial kits. All measurements with cutoff values were calculated according to the manufacturer's instructions. Any absorbance above the cutoff value was considered positive for HBsAg.

A total of 490 sera from HBsAg-positive male Saudi blood donors were tested for the presence or absence of anti-delta antibody by using com-

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mercial anti-delta radioimmunoassay kits. All measurements and cutoff values were calculated according to the manufacturer's instructions. Any absorbance below the cutoff value was considered positive for anti-delta antibody.

Results

Fifty-five of 490 HBsAg-positive sera exhibited anti-delta antibodies, indicating a prevalence of 11.2%.

Discussion

The hepatitis delta virus is a unique small RNA virus which requires HBV for its replication. The delta virus infection is endemic in the Mediterranean countries, the Middle East, Africa, and South America. In Northern Europe, the United States, and Australia, the infection is confined to parenteral drug addicts and hemophiliacs.[5-8] The mode of transmission in Northern Europe is by direct parenteral inoculation due to drug abuse or administration of commercial factor VIII and IX concentrates to hemophiliacs. In endemic areas, these mechanisms are less common and nonparenteral or inapparent; parenteral transmission appears to be an important aspect. There is undoubtedly clustering of delta infection within families,[9] suggesting intrafamilial spread of the delta virus. Vertical transmission is, at the present time, thought to be unimportant.[10]

Clinically, two modes of delta virus infection have been identified, simultaneous infection with HBV and HDV (coinfection) or delta infection in chronic HBsAg carriers (delta superinfection). In coinfection with HDV and HBV, pathogenic potential is limited by the short duration of HBs antigenemia, which HDV cannot outlive. The acute hepatitis is mainly due to the HBV component, and the pathogenic effect of HDV is relatively minor. In some cases the clinical picture may be of biphasic hepatitis with two aminotransferase peaks, the first being due to acute HBV and the second to acute HDV infection.[11] The clinical outcome is usually a fully recovery, and these individuals are not at higher risk for the development of chronic hepatitis than those infected with HBV alone.[12,13] Occasionally, combined viral infection may induce cumulative liver damage that causes severe fulminant illness.

In superinfection, the preexisting HBs antigenemia provides optimal conditions for the full expression of the HDV virulence. Clinically, this results in acute, often severe fulminant hepatitis.[14] In humans, the clinical picture depends on whether the infected subjects have previous significant HBV-related liver disease. In healthy carriers, HDV superinfection usually induces a severe acute hepatitis, and if the HBV status is unknown, it may mimic a classical acute hepatitis B. In healthy chronic carriers of HBsAg, a chronic HDV replication occurs, and these individuals are at high risk of developing severe chronic liver disease.[15] Histopathologically, a chronic active hepatitis or active cirrhosis is demonstrated in 90% of all superinfected cases of all ages.[16]

At the present time, it is believed that hepatocellular carcinoma is rare in patients with chronic hepatitis delta virus infection. This may relate to the fact that these patients have a more rapidly progressive form of liver disease and therefore do not live long enough to produce hepatocellular carcinoma.

The prevalence of anti-delta antibody in healthy HBsAg carriers in Saudi Arabia, reported as 8% (3/36) from Gizan[17] and 5.4% (7/129) by Ramia et al,[18] and 6.7% (5/75) by El-Hazmi and Ramia[19] from the Riyadh area. El-Hazmi and Ramia[19] also reported incidence of anti-delta antibody from various parts of Saudi Arabia as follows: Hofuf, 5.3% (4/75); Najran, 9.6% (5/52); Gizan, 0 (0/70), and Khaybar 0 (0/75). The previous small study from Gizan[17] reporting 8% (3/36) prevalence of anti-delta antibody contradicts the finding by El-Hazmi et al.

The present anti-delta antibody prevalence rate of 11.2% among healthy HBsAg-carrier Saudi blood donors is highest among reported rates of 8%, 5.4%, and 6.7% by Ashraf et al,[17] Ramia et al,[18] and El-Hazmi and Ramia[19] from Saudi Arabia and also 3.8%, 0.5%, and 5% from the United States,[20] and Canada,[21] and Italy.[15]

This study reemphasizes the importance of prevention of HBV (and thus HDV) by administration of the hepatitis B virus vaccine in Saudi Arabia. The considerable morbidity and mortality due to HBV and HDV infection can be prevented by successful implementation of hepatitis B vaccination program in this country.

References

1. Rizzetto M, Canese MG, Arico S, Crivelli O, et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated with hepatitis B virus in liver and serum of HBsAg carriers. Gut 1977;18(12):947-1003.
2. Rizzetto M, Canese MG, Gerin JL, London WT, et al. Transmission of hepatitis B virus-associated delta antigen to chimpanzees. J Infect Dis 1980;141(5):590-602.
3. Rizzetto M. The delta agent. Hepatology 1983;3(5):729-37.
4. Raimondo G, Smedile A, Gallo L, et al. Multicenter study of prevalence of HBV-associated delta infection and liver disease in drug-addicts. Lancet 1982;1(8266):245-51.
5. Lok ASF, Farci P, Thomas HC. Epidemiological and clinical course of delta infection in Britain. Prog Clin Biol Res 1983;143:219-33.
6. Novick DM, Farci P, Karayiannis P, et al. Hepatitis D virus antibody in HBsAg-positive and HBsAg-negative substance abusers with chronic liver disease. J Med Virol 1985;15(4):351-6.
7. Rizzetto M, Morello C, Mannucci PM, et al. Delta infection and liver disease in hemophiliac carriers of hepatitis B surface antigen. J Infect-Dis 1982;145(1):18-22.
8. Lee CA, Kernoff PB, Karayiannis P, et al. Interactions between hepatotropic viruses in patients with haemophilia. J Hepatol 1985;1(4):379-84.
9. Rocca G, Poli G, Gerardo P, et al. Familial clustering of delta infection. Prog Clin Biol Res 1983;143:133-7.
10. Zanetti AR, Ferroni P, Magliano EM, et al. Perinatal transmission of the hepatitis B virus and of the HBV-associated delta agent from mothers to offspring in northern Italy. J Med Virol 1982;9(2):139-48.
11. Caredda F, D'Arminio Monforte A, Rossi E, et al. Prospective study of epidemic delta infection in drug addicts. Prog Clin Biol Res 1983;143:245-50.
12. Smedile A, Dentico P, Zanetti A, et al. Infection with the delta agent in chronic HBsAg carriers. Gastroenterology 1981;81(6):992-7.
13. Hansson BG, Moestrup T, Widell A, Nordenfelt A. Infection with delta agent in Sweden: introduction of a new SJ, Arya SC, Arendrup M, et al. Frequencies of hepatitis B, delta and HTLV-III virus markers in Saudi Arabia. Liver 1986;6(2):73-7.
14. DeCock KM, Govindarajan S, Redeker AG. Fulminant delta hepatitis in chronic hepatitis B infection. JAMA 1984;252(19):2746-8.
15. Arico S, Aragona M, Rizzetto M, et al. Clinical significance of antibody to the hepatitis delta virus in symptomless HBsAg carriers. Lancet 1985;2(8451):356-8.
16. Rizzetto M, Verme G, Recchia S, Bonino F, et al. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of delta antigen: an active and progressive disease unresponsive to immunosuppressive treatment. Ann Intern Med 1983;98(4):437-41.
17. Ashraf SJ, Arya SC, Arendrup M, et al. Frequencies of hepatitis B, delta and HTLV-III virus markers in Saudi Arabia. Liver 1986;6(2):73-7.
18. Ramia S, El-Hazmi MA, Vivian PA, et al. Delta agent infection in Riyadh, Saudi Arabia. Trans R Soc Trop Med Hyg 1987;81(2):317-8.
19. El-Hazmi MA, Ramia S. Epidemiology of delta agent infection in Arabia: geographical distribution and prevalence of anti-delta. Vox Sang 1986;50(4):216-9.
20. Nath N, Mushahwar IK, Fang CT, et al. Antibodies to delta antigen in asymptomatic hepatitis B surface antigen-reactive blood donors in the United States and their association with other markers of hepatitis B virus. Am J Epidemiol 1985;122(2):218-25.
21. Buchner BK, Moore BP. Prevalence of delta agent among Canadian blood donors (letter). Transfusion 1986;26(4):400.

AEROBIC CAPACITY IN SAUDI ATHLETES

Mahmoud T. Kordy, MB, ChB, PhD

قيس القبط الأقصى للأوكسجين لدى واحد وعشرين رياضيا سعوديا يزاولون تدريبات غير تحمّلية (رفع الأثقال والمصارعة والملاكمة والجمنازيوم) باستخدام بروتوكول بروس متعدد المراحل. كما قيمت أيضا أوزانهم وأطوالهم والنسب المئوية لشحم الجسم. ولدى مقارنة النتائج التي حصلنا عليها مع نتائج طلبة التربية الرياضية السودانيين والرياضيين السعوديين الذين يمارسون تدريبات تحملية ظهرت فروق ذات شأن في سرعة النبض أثناء الراحة وأوزان الأجسام ولكن لم تظهر فروق في الأطوال ومستويات شحوم الأجسام. وكان قبط الأكسجين الأقصى لمجموعة الدراسة أقل كثيرا مما هو لجمهور التدريبات التحملية ولا يختلف اختلافا ذات شأن عما هو لجمهور القُعَدَة. كما كان قبط الأكسجين الأقصى لمجموعة الدراسة أقل كثيرا من المقاييس العالمية للرياضيين الذين يزاولون أنماط الرياضة نفسها. نستخلص مما سبق أن التدريبات غير التحملية لا تضع عبئا إضافيا على الجهاز القلبي التنفسي.

The maximum oxygen uptake (VO_2 max) of 21 nonendurance-training Saudi athletes (weight lifters, wrestlers, boxers, and gymnasts) was measured using the multistage Bruce protocol. Their weight, height, and percentage of body fat were also assessed. Comparison of the results obtained with endurance-training Saudi athletes and Sudanese physical education students showed a significant difference in resting pulse rates and body weights, but no difference in heights and body fat levels. The VO_2 max of the study group was much lower than that for the endurance-training population and not significantly different from a sedentary population. The VO_2 max of the study group was much lower than international standards for athletes involved in the same types of sports. It was concluded that nonendurance training does not impose an extra load on the cardiorespiratory system.

Maximum oxygen uptake (VO_2 max) is the highest oxygen consumption an individual can attain breathing air at sea level. It measures the capacity of the cardiorespiratory system to transport oxygen to all tissues, especially to the working muscles, and also the capacity of working muscles to consume oxygen. Measured under standardized conditions, VO_2 max is a reproducible individual characteristic. Moreover, VO_2 max is accepted to be the best criterion for the assessment of an individual's physical fitness or aerobic capacity.[1,2]

This report describes the physical fitness of 21 Saudi athletes. Since such measurements have not been done on Saudis, we attempted to establish baseline data necessary for follow-up of those athletes with further training and to compare the physical fitness of Saudi athletes with established international standards. Such data are useful in improving training style and prescribing adequate training programs to bring local athletes up to international standards.

Materials and Methods

Subjects

Twenty-one Saudi male subjects involved in the following athletic events were tested: weight lifting (n = 7), wrestling (n = 5), boxing (n = 5), and gymnastics (n = 4). These subjects were selected because the sports they were undertaking did not involve endurance training. The subjects had been practicing their sports for 1 to 4 years. Their phys-

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ical characteristics are presented in Table 1.

Measurement Set-Up

Three pieces of equipment were used to measure VO_2 max: (1) motor-drive treadmill; (2) the ergo-oxy-screen-system; and (3) an evaluation unit consisting of a microprocessor for acquisition and subsequent treatment of accumulated data. The evaluation unit gave half-minute on-line printouts of time, minute volume (MV) as L/min, breathing frequency as BF/min, heart rate as HR/min, volume of oxygen consumed (VO_2 max) as L/min, CO_2 output (VCO_2) as L/min, respiratory quotient (RQ), and oxygen consumption in mL/kg of body weight/min. Blood pressure was measured using a clinical sphygmomanometer. Skin-fold thickness was measured by Harpenden calipers at four sites: biceps, triceps, subscapular, and suprailiac. Total thickness in these sites was used for the calculation of percentage of body fat using special reference tables.[3]

Procedure

The exercise procedure used in this study was the multistage protocol of Bruce et al,[4] which is summarized in Figure 1. The subject, after having his resting ECG done, was fitted with a breathing mask connected to a low-resistance valve, which separated inspiratory from expiratory air flow. Expired air was passed through the pneumatograph to a breathing bag. Samples of expired air were continuously drawn and passed through calcium chloride to the gas analyzers which gave on-the-spot measurements of O_2 and CO_2 fractions. Each subject was encouraged to carry on the exercise procedure until he was completely exhausted, i.e., he attained his physiologic limit. Throughout the exercise and the first 10 minutes of recovery, the various respiratory and cardiovascular measurements (MV, BF, VO_2, VCO_2, ECG, HR, and blood pressure) were closely observed and recorded. The highest oxygen uptake in the last 3 minutes of exercise was recorded as the VO_2 max for each subject. The measurements were made on the subject's first visit to the laboratory.

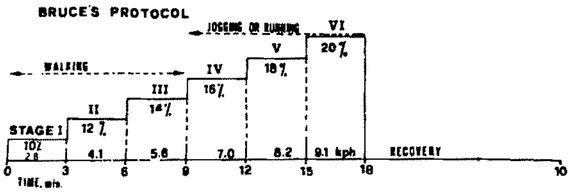

FIGURE 1. Bruce's treadmill exercise protocol. Increments of both speed (kph) and grade (%) are shown in the various exercise stages I to VI.

TABLE 1. *Physical characteristics of 21 subjects.*

Characteristic	Mean	SD	Range
Age (y)	21.0	2.9	18–30
Weight (kg)	72.2	17.3	50–121
Height (cm)	168.4	7.1	158–186
Skin-fold thickness (mm)			
Biceps	5.2	2.5	3.0–12.3
Triceps	10.5	7.9	4–33
Subscapular	13.1	10.6	4.4–26
Suprailiac	12.8	12.3	4.0–39.5
% Body fat	13.1	7.7	2.86–32.6
Fat mass (kg)	10.5	8.9	1.9–37.5
Fat-free mass (kg)	61.7	10.2	47.5–83.5

Results

Anthropometry

Table 2 shows the resting pulse rate, weight, height, and percentage of body fat of the study group. Previously published findings on endurance-training Saudi athletes[5] and Sudanese physical education students[6] are included in Table 2 for

TABLE 2. *Comparison of resting pulse, weight, height, and percentage of body fat (mean + SD).*

	Age (y)	Resting pulse rate (beats/min)	Weight (kg)	Height (cm)	% Body fat
Study group (N = 21)	21.0 ± 2.9	83.3 ± 17.3	72.2 ± 17.3	168.4 ± 7.5	13.1 ± 7.7
Endurance training group (Saudi) (N = 15)	21.2 ± 1.95	66.7 ± 6.1	61.7 ± 8.5	169.9 ± 6.4	11.1 ± 2.4
Physical education students (Sudanese) (N = 40)	21.8 ± 0.2	68.4 ± 10.3	61.6 ± 1.0	175.3 ± 1.3	14.2 ± 0.5

comparison. The three groups were males of similar ages ($P = 0.68$). The resting pulse rate ($P = 0.001$) and body weight ($P = 0.02$) were significantly higher in the study group; however, height ($P = 0.5$) and percentage of body fat ($P = 0.2$) were similar in the three groups.

Responses to Exercise

All the subjects except one were able to complete the exercise procedure up to stage V of the Bruce protocol. Their maximum values for heart rate, VO_2, and blood pressure are shown in Table 3. The VO_2 max and heart rate attained by the endurance-training Saudi subjects are also shown. Both VO_2 max ($P = 0.001$) and maximum heart rate ($P = 0.0002$) were significantly higher in the endurance-training group.

Figure 2 shows the linear relationship of oxygen consumption to heart rate of all the subjects during the performance of the treadmill exercise. The best-fit regression line and the equation describing the relationship are also presented.

The changes associated with the increase in intensity of exercise (in heart rate, VO_2, and systolic and diastolic blood pressure) are displayed in Figure 3. The line drawn joins the mean values. There were consistent changes in heart rate, VO_2, and systolic blood pressure. On the other hand, diastolic blood pressure exhibited no significant alteration. During the recovery period (Figure 2), VO_2 was back to its resting value in 5 minutes; however, the heart rate was slightly higher than the resting value at the end of the 5-minute period.

The GLIM statistical package was used to ascertain the relationships between maximum heart rate and VO_2 max and the independent variables of weight, height, skin-fold thickness, fat mass, and fat-free mass. Maximum heart rate had an R2 (correlation coefficient) of 0.46 ($P = 0.3$) with the principal correlates being fat mass and height. The VO_2 max, however, had an R2 = 0.72 ($P < 0.01$) and was correlated primarily with height (R2 = 0.75, $P = 0.005$); weight (R2 = 0.63, $P = 0.007$); fat-free mass (R2 = 0.57, $P = 0.02$); and fat-mass (R2 = 0.47, $P = 0.06$).

Step-up multiple regression analysis was used to identify the variables that accounted for the greatest variation in VO_2 max. The best equations were

TABLE 3. *Maximum heart rate, VO_2 and blood pressure (BP) attained by the subjects (stage V).*

	Maximum heart rate (beats/min)	Maximum VO_2 (mL/kg/min)	Maximum systolic BP (mm Hg)	Maximum diastolic BP (mm Hg)
Study group (N = 20)	167 ± 21.3	39.5 ± 8.18	175 ± 13.7	87.8 ± 15.0
Endurance-training group (N = 13)	194 ± 8.0	51.4 ± 8.5	190 ± 17.0	67 ± 6.0

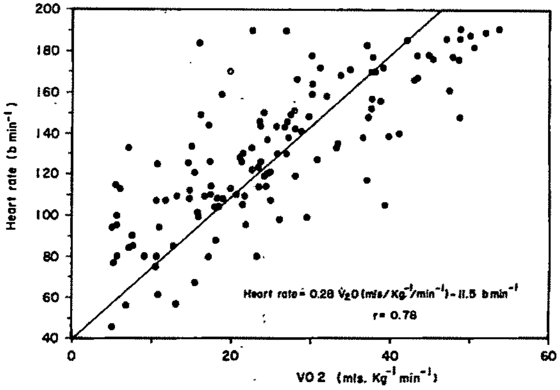

FIGURE 2. Relationship of oxygen consumption to heart rate of all the subjects during the treadmill exercise. The line drawn is the best-fit regression line. The equation describing the relationship is shown.

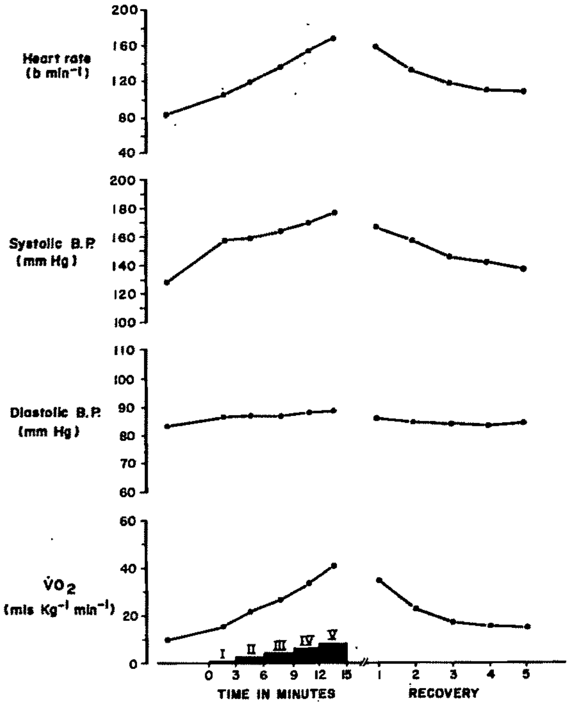

FIGURE 3. Changes in VO_2, systolic blood pressure, diastolic blood pressure, and heart rate drawn as mean values during the treadmill exercise and recovery period.

as follows: (1) VO_2 max = 65.2 height (cm) + 0.19 weight (kg) − 6.417 L/min (R2 = 0.36, $P = 0.02$); and (2) VO_2 max = 65.2 height (cm) − 12.3 fat-free mass (kg) + 6.1 fat mass (kg) − 7.367 L/min (R2 = 0.37, $P = 0.02$).

Separating weight into fat-free mass and fat mass did not improve the prediction of VO_2 max. Height on the other hand affected the variation in VO_2 max more than weight. A larger sample is needed to confirm these findings.

When VO_2 max, weight, and height between the study group and other ethnic groups were compared (Table 4), the study group had a lower VO_2 max.

Discussion

This study was an attempt to evaluate the physical fitness of Saudi athletes undertaking certain sports that do not entail endurance training, namely, weight lifting, wrestling, boxing, and gymnastics. The results indicated that the average VO_2 max is 39.5 mL/kg/min, which is markedly lower than what has been reported in endurance-training Saudi athletes and is far below the international standards for these sports.[12]

The VO_2 max is a reliable index of physical fitness. In the study reported by Keren et al[13] in 15 healthy nonprofessional athletes, the VO_2 max obtained by treadmill exercise was higher than that obtained by the bicycle ergometer or a stepping device. This justifies the use of the treadmill exercise in this study.

The maximum heart rate obtained in the study group (167 beats per minute) was lower then the expected maximum heart rate for the subjects' age group. At their age the expected maximum heart rate is nearly 200 beats per minute.[14] This may explain the lower VO_2 max obtained in the study group, i.e., subjects could possibly have continued the exercise, although all the subjects stopped exercise at stage V. Extrapolation to the expected maximum heart rate in these subjects, using the heart rate/oxygen uptake relationship, gave a VO_2 max of approximately 47 mL/kg/min.

The finding of a low VO_2 max in this group, which is not significantly different from an untrained population, agrees with the work of Lehmann and Keul,[15] where the VO_2 max for eight weight lifters was 47.2 ± 5.6 mL/kg/min and that for an untrained group of nine subjects was 46.7 ± 9.4 mL/kg/min. Hukkinen et al[16] found a VO_2 max of 41.9 ± 7.2 mL/kg/min in weight lifters. In addition, Stone et al,[17] examining weight lifters trained for 8 weeks, found a mean VO_2 max of 42.4 mL/kg/min. The findings of this study suggest that nonendurance training does not impose an extra load on the cardiorespiratory system beyond that required for sedentary life.

The highly significant correlation of VO_2 max

TABLE 4. *Comparison of VO_2 max and other physical characteristics between Saudi subjects and other ethnic groups.*

	N	Age (y)	Height (cm)	Weight (kg)	VO_2 max (mL/kg/min)
Saudis[5]	16	28.4 (20–39)	171.3 (164–180)	72.6 (54–94)	39.9 (29.3–50.9)
Study group	21	21 (18–30)	168.4	72.2 (50–121)	39.5 ± 8.18
Italians[7]	12	21–30	160–180	58–79	39–49
Norwegians[8]	26	23.4 ± 5.3	177.3 ± 5.9	73.1 ± 2.2	44.1 ± 3.9
Americans					
Busherk and Taylor[9]	26	22.5 ± 2.8	177 ± 6.2	78.6 ± 16.9	44.6 ± 5.5
Hermansen et al[10]	4	19–21	180–184	62–73	54
Wyndham et al[11]					46–61
South Africans					
Caucasians	7	30 (24–39)	175.9 ± 7.7	79.2 ± 9.3	39.1 ± 1.78
Bantus	26	18–25	165.9 ± 6.0	59.1 ± 6.0	41.3 ± 2
Bushmen	3		160.5 ± 6.0	51.4 ± 5.2	47.1 ± 6.9

with body weight was expected. However, stature also had a highly significant correlation with VO_2 max, which cannot be explained at present.

Novak et al[12] commented, "It seems that each type of athletic activity with its demand for a certain kind of functional performance may modify the body composition of an athlete according to what is most suitable for such activity." This statement may support the finding in this study group where body weights in athletes participating in nonendurance activities were significantly higher than in those endurance-training athletes.

References

1. Astrand PO. Aerobic work capacity during maximal performance. Circ Res 1967;20(suppl):201-10.
2. Willmore JH. Acute and chronic responses to exercise. In: Amsterdam EA, et al, eds. Exercise in cardiovascular health and disease. New York: Yorke Medical Books, 1977:53-69.
3. Durin JV, Womersley JV. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1974;32:77-97.
4. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment and cardiovascular disease. Am Heart J 1973;85:546-62.
5. Gader AMA, Hussain A, Kordy MT, Zainul Abedin M. Aerobic capacity (physical fitness) of healthy Saudi subjects. Proceedings of Dammam Conference, 1983:23-31.
6. Ballal MA, Fentem PH, Macdonald IA, et al. Physical condition in young adult Sudanese: a field-study using a self-paced walking test. Ergonomics 1982;25(12):1185-96.
7. Prampero DPC, Davies TM, Cerretlli O, Margona R. An analysis of oxygen debt contracted in submaximal exercise. J Appl Physiol 1970;29:547-51.
8. Hermansen L, Anderson KA. Aerobic work capacity in young Norwegian men and women. J Appl Physiol 1963;20:425-31.
9. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition with special reference to chronic physical activity and obesity. J Appl Phsyiol 1965;11:72-8.
10. Hermansen L, Ekblom B, Saltin B. Cardiac output during submaximal and maximal treadmill and bicycle exercise. J Appl Physiol 1970;29:82-6.
11. Wyndham CH, Strydom NB, Morrison JE, et al. Differences between ethnic groups in physical working capacity. J Appl Phsyiol 1963;18:361-6.
12. Novak LP, Hyatt RE, Alexander JF. Body composition and physiologic function of athletes. JAMA 1968;205:764-70.
13. Keren G, Magazanik A, Epstein Y. A comparison of various methods of the determination of VO_2 max. Eur J Appl Physiol 1980;45(2-3):117-24.
14. Jones NL, Campbell M. Clinical exercise testing. 2nd ed. Philadelphia: WB Saunders, 1982:34.
15. Lehmann M, Keul J. Free plasma catecholamines, heart rates, lactate levels, and oxygen uptake in competition weight lifters, cyclists, and untrained control subjects. Int J Sports Med 1986;7(1):18-21.
16. Hukkinen K, Alen M, Komi PV. Neuromuscular anaerobic and aerobic performance characteristics of elite power athletes. Eur J Physiol 1984;53:97-105.
17. Stone MH, Wilson GD, Blessing D, Rozenek R. Cardiovascular responses to short-term olympic style weight-training in young men. Can J Appl Sport Sci 1983;8(3):134-9.

PREVALENCE OF INTESTINAL PARASITES AMONG PATIENTS IN THE ABHA REGION

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أجريت دراسة استعادية على مرضى مركز شمسان للرعاية الأولية لتقصي مدى انتشار الطفيليات المعوية بالنسبة إلى العمر والجنس والفصلية. شملت الدراسة جميع المرضى الذين أجرى لهم فحص عينات البراز خلال عامي ١٤٠٦هـ و١٤٠٧هـ (١٩٨٥ ـ ١٩٨٧) وتم تسجيل النتائج بدقة. أشارت النتائج إلى أن نسبة ٢٪ من إجمالي المرضى وعددهم ٢٨٣٦٢٢ قد أبلغوا بنتائج فحص عينات البراز. كان المعدل الإجمالي لانتشار الطفيليات يساوي ٢٩,٤٪. كانت جميع الأعمار والأجناس مضابة بالطفيليات في خين كانت معدلات الانتشار أعلى بين الأطفال دون العاشرة من العمر وفي الإناث من سن ٢٠ إلى ٤٩ عاما. كانت هنالك اختلافات فصلية في معدلات انتشار الطفيليات. كان معدل انتشار الجياردیات اللامبلية ١٥,٥٪، الأميبة الحالة للنسج ٧,٥٪؛ والعصيات القولونية ٦,٢٪، والصفر الخراطيني ١٪، والمحرشفة القزمة والمنشقة أقل من ١٪. ولم نشهد وجود الذودة الشصية. كان من المتوقع أن تكون الجياردیات اللامبلية أقل تواردا، إلا أنه بدا أن معدل انتشارها في الطقس الجاف وفي مرتفعات منطقة أبها (٢٥٠٠ إلى ٣٠٠٠ مترا) أكثر من المعدلات السائدة في الأجواء الأخرى في المملكة أو مماثل لتلك المعدلات.

A retrospective study was conducted among the patients of the Shamasan Primary Health Centre to find the prevalence rates of intestinal parasites by age, sex, and seasonality. All patients whose stool samples were examined and properly recorded during the years 1406H and 1407H (1985-87) were included in the study. Results showed that about 2% of the 283,622 patients were advised stool analysis. The overall parasite prevalence rate was 29.4%. All ages and sexes were affected, with higher prevalence rates in children less than 10 years of age and in females aged 20 to 49 years. There were some seasonal variations in the parasite prevalence rates. The prevalence rate for *Giardia lamblia* was 15.5%, *Entamoeba histolytica* 7.5%, *E. coli* 6.2%, *Ascaris lumbricoides* 1%, and *Hymenolepis nana* and *Schistosoma* less than 1%. Hookworm was not seen. Although a lower prevalence rate of *G. lamblia* was expected, its prevalence rate in the dry atmosphere and high altitude (2500 to 3000 meters) of the Ahba region appears to be higher than or similar to that in other parts of the Kingdom.

Most intestinal parasites have been associated with ill health for centuries. The prevalence of almost all parasites depends on climatic and socioenvironmental conditions. In a Bangladesh slum, over 80% of the population have one or more parasites.[1] In some parts of India, *Ascaris* infection has been reported to vary from 80% to 95%.[2] In Pakistan, the prevalence of parasites in diarrheal patients was found to be 71%, with a

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high rate of *Giardia lamblia*.[3] In one community of Canada, the *A. lumbricoides* prevalence rate was over 28%.[4] In Yemen, a neighboring country of Saudi Arabia, 53% of the stool specimens were positive for intestinal parasites.[5] At the same time, only 7.56% of the food handlers working in restaurants of Saudi Arabia were infested with parasites, and a very low percent of them had *Entamoeba histolytica* (3.17%) and *G. lamblia* (3.10%) infection.[6] But the prevalence rates were different in expatriates working in Riyadh. Among them, 55.7% were infested with parasites.[7] In another hospital-based study in Riyadh, 22.9% of the patients had pathogenic parasites and many more commensals.[8]

It thus appears that the parasite rate varies from country to country, and even among different parts and different populations of the same country. The parasite prevalence rates of Abha, which is situated at a high altitude (2500 to 3000 meters), have not been adequately documented. We, therefore, conducted a retrospective study to examine the pattern of parasites and their prevalence rate in patients attending the Shamasan Primary Health Centre of Abha City. Our aim was to understand the age and sex distribution of patients and the topographic and climatic influence on parasite prevalence rates.

Materials and Methods

Shamasan Primary Health Centre is one of the three health centers in Abha City. Patients are treated irrespective of their religion and nationality. Patients having complaints suggestive of association with parasitic infection were referred by all physicians of the center to the clinical pathology laboratory for stool examination. Plastic stool cups with tight lids were supplied to patients, and fresh stool samples were received on the subsequent mornings for examination. Specimens underwent microscopic examination quickly using a saline and iodine stained wet-mount preparation, according to the standard method recommended by the WHO.[9] Both cysts and vegetative forms of *G. lamblia* and *E. histolytica* were considered as positive findings.

Analysis has been done with consideration to age, sex, and seasonality. Each month represents 2 months' data of the Hejira years 1406 and 1407 (1985-87). All results of stool examination (5398) were included in the analysis, except some cases where age and sex were ill defined. Official holidays and leave days of the examiner were not covered. Significance was tested by using the chi-square test where necessary.

Results

During the 2-year period, 283,622 patients attended the Shamasan Primary Health Centre for treatment, and 5398 patients' stool specimens (1.9%) were examined. On the whole, approximately 10 stool samples were tested per clinic-day in addition to urine, blood, and other samples. Of 5398 stool specimens examined, 1586 (29.4%) were positive for parasites.

The age and sex distribution of the patients contracting parasites is shown in Table 1. The distribution was not uniform for all ages. The rates were lower in patients 15 to 19 years old for both sexes compared to the other age groups. This difference was statistically significant ($P < 0.05$). The prevalence rates in patients up to 10 years old and in females between the ages of 20 and 49 years were higher than in other age groups. These differences were also significant statistically ($P < 0.01$ and < 0.05, respectively). The overall rates between males (29.3%) and females (29.5%) were not different. In patients age 50 and over, females had a lower rate (22.3%) than males (32.6%), though this difference was not statistically significant.

Prevalence of *Ascaris*, *Schistosoma mansoni*, and *Hymenolepis nana* was equal to or less than 1% (Table 2). No hookworm was isolated from 5398 stool samples. The overall prevalence rate of *G. lamblia* was higher (15.5%) than any other pathogens. Its prevalence rate in children less than 10 years of age was higher than any other age groups in both sexes ($P < 0.001$). The prevalence of *E. histolytica* (7.7%) and *E. coli* (6.2%) was almost uniform in all age groups. The rates were not significantly different between males and females.

There was no significant seasonal variation in the prevalence of *G. lamblia*, but the prevalence rate of *E. histolytica* during December and January was significantly higher than the prevalence rate for February and March ($P < 0.05$). The

TABLE 1. *Prevalence of* Lamblia, E. histolytica *and* E. coli *by age and sex of patients.*

	Male					Female				
Age (y)	Total tested	*G. lamblia* No. (%)	*E. histolytica* No. (%)	*E. coli* No. (%)	All parasites No. (%)	Total tested	*G. lamblia* No. (%)	*E. histolytica* No. (%)	*E. coli* No. (%)	All parasites No. (%)
< 5	636	165(25.9)	59(9.3)	19(3.0)	243(38.2)	446	92(20.6)	28(6.3)	16(3.6)	136(30.5)
5 – 9	535	105(19.6)	46(8.6)	35(6.5)	185(34.6)	428	97(22.7)	26(6.1)	28(6.5)	151(35.3)
10 – 14	331	58(17.5)	21(6.3)	20(6.0)	99(29.9)	242	42(17.4)	12(5.0)	21(8.7)	75(31.0)
15 – 19	160	18(11.2)	10(6.2)	12(7.5)	40(25.0)	116	16(13.8)	1(0.9)	8(6.9)	25(21.6)
20 – 29	648	62(9.2)	65(10.0)	34(5.2)	161(24.8)	433	45(10.4)	38(8.8)	33(7.6)	46(26.8)
30 – 39	477	36(7.5)	38(8.0)	29(6.1)	103(21.6)	321	38(11.8)	25(7.8)	27(8.4)	90(28.0)
40 – 49	249	16(6.4)	22(8.8)	16(6.4)	54(21.7)	129	20(15.5)	5(3.9)	13(10.1)	38(29.5)
50 – 59	82	10(12.2)	6(7.3)	9(11.0)	25(30.5)	59	5(8.5)	5(8.5)	2(3.4)	12(20.3)
> 60	53	6(11.3)	7(13.2)	6(11.3)	19(35.8)	53	5(9.4)	4(7.5)	4(7.5)	13(24.5)
Total (%)	3171	476(15.0)	274(8.6)	180(5.7)	930(29.3)	2227	360(16.2)	144(6.5)	152(6.8)	656(29.5)

The parasite prevalence rate in children under 10 years of age is higher than for all other age groups, and the prevalence rate in females between the ages of 20 and 49 years is higher than that for males of the same age group ($P < 0.05$).

TABLE 2. *Prevalence of parasites among 3171 males and 2227 females tested.*

	Male	Female	
Parasites	No. positive (%)	No. positive (%)	Total
G. lamblia	476(15.01)	360(16.16)	836(15.48)
E. histolytica	274(8.64)	144(6.46)	418(7.74)
E. coli	180(5.67)	152(6.82)	332(6.15)
A. lumbricoides	43(1.35)	15(0.67)	58(1.07)
H. nana	24(0.75)	22(0.98)	46(0.85)
Schistosoma	20(0.63)	4(0.17)	24(0.44)
Hookworm	0(0.0)	0(0.0)	0(0.0)
Total	1017(32.07)	697(31.29)	1714(31.75)

overall rate for *G. lamblia* (15.5%) was twice the rate of *E. histolytica* (7.7%).

Discussion

About 2% of patients are usually referred for stool testing. The reasons for high and low rates of stool microscopy during Safar (September-October) and Jumada Al-Awal (December-January) in this study are not evident. Diarrheal diseases, however, increase from the month of Safar (October) in Southeast Asian countries. The exact seasonal trend in Saudi Arabia, especially in Abha, is not known. The higher or lower percent of stool testing does not coincide with the higher or lower percent of stool positivity. Therefore, to find out all agents associated with intestinal symptoms, further investigation by doing both stool microscopy and stool culture is necessary.

The rate of isolation of parasites in children under 10 years old is significantly higher than those over 10. The higher rates of isolation in females than males 20 to 49 years old may be due to their physical exposure to ill children and their excreta. The low rate in the group 15 to 19 years old may be due to better personal hygiene and less exposure to child care before reaching the parental stage.

Giardia is more often found in fecally contaminated water.[10] In Abha, people use bottled and jar water for drinking and dug well water for washing and bathing. Although transmission through dug well water and contaminated vegetables cannot be ruled out, there is a greater possibility of transmission from person to person. Recently, zoonotic transmission has been suggested for giardiasis,[10] but its possibility in Abha is remote for its low animal population and absence of beavers. From the almost uniform seasonal prevalence of both *G. lamblia* and *E. histolytica*, it appears that there are no major seasonal factors which might increase or decrease transmission in this community.

During the same period (1987), Madani and associates isolated 3.5% of *G. lamblia* from 722 apparently healthy individuals of the same city (personal communication). Our isolation rate of *G. lamblia* in the primary health center patients was much higher (15.5%), and this difference is highly significant statistically ($P < 0.001$). It may, therefore, be inferred that, although there may be some inapparent infections like many other intestinal pathogens, *G. lamblia* is primarily associated with abdominal symptoms. No such difference has been observed in these two samples in the isolation rates of *E. coli* (6.2% vs 7.6%). In about 5% of cases, however, mixed infection was noticed.

The total absence of hookworm in this population is interesting. Since the people do not walk barefooted, the endemicity is unlikely. The environment may be detrimental even for sporadic occurrence of hookworm. The low prevalence (1%) of *A. lumbricoides* is remarkable. In other areas of the Kingdom[8] and other Arab countries,[5] the rates were higher. Lack of surface water, use of latrines, and presence of dry weather may be detrimental to these parasites' existence. Selection of samples may also influence the prevalence rate. Further research is needed to determine the modes of transmission of *G. lamblia* among these patients living in this dry place situated at a high altitude.

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References

1. Khan MU, Shahidullah M, Barua DK, Begum T. Efficacy of periodic deworming in an urban slum population for parasite control. Ind J Med Res 1986;83:82-8.
2. Elkins DB, Haswell-Elkins M, Anderson RM. The epidemiology and control of intestinal helminths in the Pulicat Lake region of Southern India: I. Study design and pre- and post-treatment observations of Ascaris lumbricoides infection. Trans R Soc Trop Med Hyg 1986;80(5):774-92.
3. Baqai R, Zuberi SJ. Prevalence of intestinal parasites in diarrhoeal patients. J Pak Med Assoc 1986;36:7-11.
4. White FM, Pereira LH, Embil JA, Manuel FR. *Ascaris* lumbricoides in Nova Scotia. Can J Public Health 1986;77(3):201-4.
5. Farag HF. Intestinal parasitosis in the population of the Yemen Arab Republic. Trop Geogr Med 1985;37(1):29-31.
6. Khan ZA, Al-Jama AA, Madan I. Parasitic infections among food handlers in Dammam and Al-Khobar, Saudi Arabia. Ann Saudi Med 1987;7(1):47-50.
7. Abdel-Hafez MA, El-Kady N, Noah MS, et al. Parasitic infestation in expatriates in Riyadh, Saudi Arabia. Ann Saudi Med 1987;7(3):202-6.
8. Qadri SMH, Khalil SH. Intestinal parasites: incidence and etiology in over 1,000 patients at King Faisal Specialist Hospital in Riyadh. Ann Saudi Med 1987;7(3):207-11.
9. Willis. Manual of basic techniques for a health laboratory. Geneva: WHO, 1980;163.
10. Bemrick WJ, Erlandsen SL. Giardiasis: is it really a zoonosis? Parasitol Today 1988;4(3):69-71.

Special Communication

CUTANEOUS CAUTERY (AL-KOWIE): A STUDY IN A PEDIATRIC OUTPATIENT CLINIC IN CENTRAL SAUDI ARABIA

Hugh G. Watts, MD

كي الجلد وسيلة تقليدية للعلاج تمارس في المملكة العربية السعودية على نطاق واسع وقد صادفنا خلال فترة أحد عشر شهرا سبعة وستين ممن أجري لهم الكي من بين ٢٩٨ من المراجعين الجدد (٢٢٪) في عيادة جراحة العظام لدى الأطفال. وجرى سؤال والديهم بوساطة استبيان. كانت أكبر نسبة علاج بالكي لدى مجموعة شلل الأطفال، وعلى الرغم من كون مجموعة خلل النماء العصبي أكبر من مجموعة الشلل إلا أن من تعرضوا للكي من أفرادها كانوا أقل عددا، وبدا أن لا تأثير للمستوى التعليمي للوالدين على قرار اللجوء إلى الكي بينما كثيرا ما كان لأجداد المرضى تأثير في هذا القرار. وكان اللجوء إلى الكي يتم غالبا بعد العلاج الطبي المعتاد، ولكن غالبية الوالدين شعروا بأن الكي لم ينجع.

Cutaneous cautery is a traditional therapeutic technique practiced widely in Saudi Arabia. During an 11-month period, in a pediatric orthopedic clinic, 67 of 298 new patients (22%) were seen who had had cutaneous cautery. Their parents were interviewed by questionnaire. The largest proportion of cautery treatments had occurred in patients with polio. Though the group of patients with neurodevelopmental disorders outnumbered polio patients, less had had cautery. The parents' educational level did not seem to affect the decision to seek cautery treatment, and the patients' grandparents were often influential in the decision for cautery. Cautery was generally sought after conventional medical treatment, and the majority of parents felt that the cautery did not help.

The use of cutaneous cautery for the treatment of varied ailments is as old as time. For physicians who are not accustomed to dealing with this entity, particularly when the patients are children, the presentation of an infant with multiple scars can be an upsetting event. If the cutaneous cautery interferes with the patients' medical care (such as multiple infected cautery sites in a child on chemotherapy), the frustration may turn to anger directed at the parents.

It is unlikely that such native medical practices will disappear in a short time, so it is important for physicians to understand the treatment and the perception of patients or their relatives.

It was with these factors in mind that a study of cutaneous cautery in patients seen in the pediatric orthopedic clinic at King Faisal Specialist Hospital was instituted.

Materials and Methods

All new patients presenting to the pediatric orthopedic clinic from 1 January 1988 until 1 November 1988 were studied. During this interval, 298 new patients were seen, and their parents interviewed by questionnaire. While a number of these patients are not children, they have diseases which fall under the expertise of a pediatric orthopedic surgeon. The questions were asked by an Arabic-speaking nurse or paramedical worker, and the forms filled in by these personnel. The child's age and sex were noted, and whether or not the child had received cautery. Also recorded were the highest levels of schooling attained by

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both the father and mother (either none, grade school, high school, or university).

If the child had received cautery, the parents were further asked whether the cautery had taken place before or after the child had been seen by a physician in a clinic or hospital. They were asked whether the person doing the cautery was male or female, "old" or "young" ("old" and "young" were not further defined), and by what method the cautery was done. They were asked the number of treatments, whether the treatment helped, and if so, in what way. They were asked who decided the patient should undergo the treatment, the parents, grandparents, other relatives, or someone not a family member. Finally, they were asked how much money was paid for each session. The child's diagnosis, the onset age of the disease, and the location of cautery were recorded by the orthopedic surgeon.

Results

Of the 298 children, 67 (22%) had received cautery. The mean age of the children who received cautery was 10.0 years, and for those who did not receive cautery, it was 7.1 years. The percentage of patients over 15 years who had received cautery was 19% and for those who did not receive cautery 5% (significant at 0.1%). The percentage of patients under 1 year of age who received cautery was 3%, while for those who did not receive cautery the percentage was 12% (significant at 1%).

There was no significant difference between the two groups of patients' parents when comparing those with no education against those with some education (Tables 1 and 2).

Patients with polio had cautery more frequently than other patients; 56% of patients with polio had had cautery. Thirty-seven percent of patients with neurodevelopmental disorders, such as cerebral palsy, congenital hydrocephalus, congenital hypotonia, and post-traumatic CNS dysfunctions, had cautery (Table 3).

The mean duration of symptoms in patients who had had cautery was 7.6 years, while it was

TABLE 1. *Parental education.*

Educational level	Cautery*		No cautery*	
	Father	Mother	Father	Mother
None	44%	69%	32%	56%
Grade school	28%	23%	30%	22%
High school	11%	5%	18%	14%
University	17%	3%	20%	7%

* There was no significant difference between the "cautery" and "no cautery" groups.

TABLE 2. *Parental education.*

Educational level	Cautery	No cautery
Both parents with no education	44%	30%
Both parents with either grade school or high school	36%	48%
Father only had university	16%	14%
Mother only had university	2%	1%
Both father and mother had university	2%	7%

TABLE 3. *Diagnoses.*

Diagnosis	No. of patients without cautery	No. (%) of patients with cautery
Polio	15	19 (56)
Neurodevelopmental disorders*	47	28 (37)
Morquio's disease	4	2 (33)
Old infections	2	1 (33)
Bone dysplasias†	10	4 (29)
Myopathy††	10	3 (23)
Bow legs/in toe/knock knee	6	1 (14)
Tumor	7	1 (13)
Congenital hip dysplasia	36	4 (10)
Scoliosis	9	1 (10)
Erb's palsy	11	1 (8)
Congenital anomalies	30	1 (3)
Club feet	7	0
Post-traumatic paraplegia	3	0
Trauma-related disorders	9	0
Legg-Perthes disease	4	0
Neurofibromatosis	3	0
Myelodysplasia	8	0
Arthrogryposis	3	0
Miscellaneous	7	1 (13)
Total	231	67 (22)

* Includes cerebral palsy, congenital hydrocephalus, congenital hypotonia, post-meningitis and post-encephalitis dysfunctions, and post-traumatic CNS dysfunctions.

† Includes osteogenesis imperfecta, vitamin-D-resistant rickets, and congenital dysplasias.

†† Includes Duchenne's myopathy, congenital myopathies, Kugelberg-Welander disease, and Werdnig-Hoffmann disease.

6.1 years in patients without cautery. In patients whose symptoms had been present for less than 1 year, 7% had had cautery and 22% had not. The distribution of patients with symptoms present for less than one year is significantly different at the 1% level.

Of the patients who had cautery, 53% were male and 47% female. Of those who did not have cautery, 56% were male and 44% female.

Among the 67 children who had cautery, the parents decided on the treatment in 65%, while the grandparents made the decision in 20%, other relatives in 12%, and unrelated persons in 3%.

If the grandparents made the decision, 31% of the parents had university education. If the parents themselves decided, only 13% had university education. Of 16 patients from the total group where both parents had university education, only one had cautery and that was decided on by the grandparents. Of two patients where mother only had university education, one had cautery, and the decision was made by the grandparents. Of all patients with one or both parents with university education, 21% had cautery, which was the same proportion as the entire group. Yet the decision in these patients was made by grandparents in 67% (while grandparents decided overall in only 20%).

In 24%, cautery was administered before seeing a doctor in a hospital or clinic. In 73%, it occurred after the doctor visit, and 3% had cautery both before and after.

The practitioner who administered cautery was male in 46% of cases and female in 54%. Ninety-eight percent of the parents perceived the practitioner to be "old."

Most parents described the cautery as being done with hot metal or an iron rod which had been placed in the fire. One practitioner had used a stick of burning wood, another a hot pin, and a third used a lighted cotton-tipped applicator.

Several parents stated that the cautery was accompanied by the child's eating some plants or drinking some plant juice, as well as the rubbing in of ointments. One parent stated that the cautery was done while the child was fasting, and immediately following this, the child was ordered to drink a glass of milk.

Roughly speaking, the location of cautery was related to the areas of illness. Children with polio had their cautery scars over the affected limbs. Children who had cerebral palsy tended to have their scars at the midline of the spine or on the head. Many children had additional scars in a rosette around the umbilicus of the abdomen. Patients without localization of symptoms to one side or the other tended to have their scars symmetrically placed about the midline.

The number of treatments ranged from one to 20. Thirty-nine children (58%) received only one treatment; four received two treatments; five children received three to six treatments; one child with severe total body cerebral palsy received 10 treatments; one child with spinal muscular atrophy received 20 treatments. For 17 children, the parents did not know or remember the number of treatments.

Seventy-eight percent of parents felt that the cautery did not help. In 13% of children, the parents felt that it had helped considerably, while in another 9%, they felt that it had helped somewhat. Children whose parents felt that the treatment had been in some way successful all had only one treatment session. The parents thought that the cautery had helped in one patient with polio, both of whose legs had been involved. After the cautery, the right leg had improved, but the left remained the same. In other patients with polio, shortness of breath improved in one and another child was able to walk after the cautery. After treatment for metabolic encephalitis (severe total body involvement), the child moved her limbs somewhat for 15 days. With treatment for hydrocephalus, the parents reported that the child felt better. In a patient with cerebral palsy with seizures, cautery stopped the movement in her eyes. In another patient with cerebral palsy, the child seemed to become more healthy.

Sixty-four percent of the parents stated that they did not have to pay anything for the treatments. The remainder paid from SR1 to SR2000 per treatment (with a mean of SR 737). The parents of the child who had 20 treatments and the one with 10 treatments both stated they paid SR2000 for each treatment. The aggregate cost of these treatments for all patients was SR71,300.

Several parents stated that there was no fixed cost, but they were expected to pay whatever they wanted to or could afford. A number of parents were somewhat evasive when answering this question.

Discussion

Because the pediatric orthopedic clinic at KFSH is a referral center for tertiary care problems, this study is biased toward patients with chronic diseases that have little likelihood of spontaneous remission (except for three of the patients with poliomyelitis who had cautery soon after the development of the disease, when spontaneous improvement could be expected). In spite of this patient bias, over 20% of the parents felt that their children benefited from the cautery treatments. As long as parents continue to perceive that such treatments will help their children, it can be expected that this type of medical treatment will continue. While these parents perceived the treatments to be helpful, the beneficial effects cited by the parents were mostly marginal. It is curious that none of these patients with partial improvement returned for more treatments in hope of enhancing the small gains.

The cost of the treatments gives some indication of the value of cautery therapy as perceived by the children's families. In addition, the aggregate cost of over SR70,000 indicates that this needs to be considered by economists when they are estimating the cost of health care in the Kingdom.

The patients who did not receive cautery were slightly younger, and there was a larger proportion whose symptoms had been present for a shorter time (i.e., less than 1 year). Possibly, patients who have problems of shorter duration would seem less hopeless to their parents, and therefore the parents might be less likely to search for alternative treatments.

It is of particular importance that the majority of patients receiving cautery did so after they had already been seen in modern medical facilities. Cautery, therefore, is not a first line of defense to be used followed by a consultation with a medical doctor when the cautery fails, but quite the contrary. This is in keeping with the old Arabic saying that cautery is reserved as a last resort. Therefore, cautery will probably continue in one form or another for a long time.

The continued reliance on cautery reflects the parents' disappointment with modern medical care. In part, this may be due to overly high expectations of what is possible. Perhaps if physicians spent more time explaining to patients or their relatives the nature of the disease and appropriate expectations, the never-ending search for a cure-all for many of the chronic diseases could be decreased.

The role of the level of education of the parents is not clear. The high overall incidence of parents having no education is presumably representative of the rapidly changing social situation in Saudi Arabia. The education of the parents of those children who received cautery was not significantly different from those who did not. The father alone having had a university education did not greatly decrease the likelihood of having cautery while both father and mother with university education did have a significant impact. For children of the university-educated parents, the decision for cautery was more likely to have been made by the grandparents than the parents. Whether this is true, or whether such parents felt the need, when interviewed, to blame others is not known.

Since the education of parents is not a striking factor in the decision for undergoing cutaneous cautery, it is probable that the marked increase in the number of Saudis with schooling will not likely alter the incidence of children receiving cautery in the near future.

Clinical Review

COMPARATIVE PATHOGENESIS OF ANIMAL AND HUMAN RETROVIRUS INFECTIONS

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تشترك حمة نقص المناعة الآدمية في بعض السمات البنيوية والبيولوجية مع الحمات البطيئة الأخرى مثل حمات ميدي وفيسنا وفقر دم الخيل الخمجي. فعملية التبرعم وبنية لب الحمية متشابهتان. وهما يشتركان أيضا في طول فترة الحضانة التي قد تمتد شهورا أو سنوات، وفي تبدل مستضدات البروتينات السكرية على غلاف الحمة. بالإضافة إلى ذلك، تؤيد بعض العلاقات المستضدية والجينية التكهنات القائلة بأن حمات ميدي وفيسنا وفقر دم الخيل الخمجي قد تكون أسلافا مشتركة لحمة نقص المناعة الآدمية. غير أن التحليل المقارن لأمراض الحمات البطيئة الآدمية والحيوانية، وخاصة خلاياهما المستهدفة، ومقارنة تسلسل الأسس لم يظهرا نقطا تشابه فحسب بل أظهرا فروقات ملحوظة بينهما أيضا.

The human immunodeficiency virus (HIV) shares some structural and biological features with other lentiviruses such as maedi, visna, and equine infectious anemia viruses. Both the budding process and the structure of the virus core are similar. They also share long incubation periods which may be months or years and an antigenic drift of the viral envelope glycoproteins. In addition, some antigenic and genetic relationship has favored speculations that maedi and visna or equine infectious anemia viruses may be common ancestors of HIV. A comparative analysis of the pathogenesis of human and animal lentiviruses, especially their corresponding target cells, and a sequence comparison revealed similarities but also remarkable differences among them.

Retroviruses were initially discovered as agents associated with cancer. Today, however, it is evident that they also cause inflammatory and immunologic disorders, which result in a variety of clinical diseases, while the vast majority is considered to be nonpathogenic.

The family Retroviridae comprises about 50 viruses. Its name was derived from the enzyme reverse transcriptase, a DNA polymerase, which is essential for the transcription of viral RNA into a complementary DNA (the so-called provirus). The family Retroviridae is divided into three subfamilies:

1. The Oncovirinae, which comprises all known oncogenic RNA viruses (e.g., feline, avian, and murine leukemia viruses).
2. The Spumavirinae, isolated from a variety of cells and considered nonpathogenic.
3. The Lentivirinae, the so-called slow viruses, known for their long incubation period and the insidious progress of the disease. This subfamily has received great attention in the last few years after the discovery of the human immunodeficiency virus (HIV, formerly called HTLV-III), the etiologic agent of human acquired immune deficiency syndrome (AIDS) and its subsequent identification as a lentivirus. Some of the best characterized lentiviruses are maedi and visna viruses of sheep, which induce a chronic pneumonia and a progressive neurologic impairment, respectively. Equine infectious anemia virus causes a chronic disease with immune-complex-mediated anemia, jaundice, and alterations of the capillary endothelium.

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Associated Diseases

Several diseases are associated with important animal and human retrovirus infections.

Leukemia/Lymphoma

Most type C oncornaviruses replicate in metabolically active cells like bone marrow. The corresponding tumors commonly arise in cells of mesodermal origin (lymphomas, leukemias, fibrosarcomas, etc.). Leukosis and/or lymphomas are associated with avian and feline leukemia viruses, although with the latter, true leukemia is a rare event.[1] HTLV-I and HTLV-II are the causative agents of adult T-cell and hairy cell leukemias, respectively.[2] Enzootic bovine leukosis is caused by bovine leukemia virus and is the most common neoplasm in cattle.[3]

The full-blown picture of human AIDS is frequently associated with neoplasms, particularly of the Kaposi sarcoma type, but it is not confirmed whether HIV is the etiologic agent of this tumor. It is accepted that HIV-induced immune suppression enables other viral or opportunistic agents to develop their pathogenic potentials, which otherwise are suppressed.[4]

Immunosuppression/Immunodeficiency

Impaired immunity is often associated with retrovirus infection, particularly with feline leukemia virus infection, and even the term "FAIDS" was introduced to describe this condition. Pedersen et al[5] described a feline T-lymphotropic lentivirus with immunosuppressive properties. Recently, a T-lymphotropic lentivirus was isolated from a persistently leukopenic cat with mild lymphadenopathy.[6] It is not yet known if both viruses are antigenically related.

Alterations of the immune system are also seen after infection with bovine leukemia virus, e.g., decreased T-lymphocyte numbers, diminished responsiveness to newly encountered antigens, or production of immunoglobulins with impaired structural and biological reactivities.[7] In vivo data are complemented by in vitro studies showing an inhibition of different immune functions by cattle infected with the bovine leukemia virus.[8] A bovine immunodeficiency-like virus, isolated from the leukocytes of cattle with lymphadenopathy and progressive weakness, was described recently,[9] which displays a genetic relationship and biological similarity to HIV. Immunodeficiency is the hallmark of HIV infection; some mechanisms will be mentioned later.

Anemia

Anemia is frequently associated with avian and feline leukemia virus infections. In the latter disease, anemia may be hemolytic (immune complex mediated) or hypoplastic (depressed hematopoiesis), presumably caused by selective suppression of erythroid precursors.[10]

Anemia caused by infection with the equine infectious anemia virus is the prominent clinical symptom of equine infectious anemia.[11,12] The underlying mechanism can be regarded as an autoimmune phenomenon and will be described later.

Pneumonia

Chronic interstitial pneumonia is the main manifestation of maedi virus infection; it can also be seen in goats with caprine arthritis-encephalitis.[13] A chronic interstitial pneumonitis in adult sheep is the ovine progressive pneumonia,[14] caused by a nononcogenic retrovirus that is similar, but not identical to, the maedi virus. The lungs are commonly affected in AIDS patients. Pulmonary manifestations include both opportunistic (e.g., *Pneumocystis carinii* pneumonia) and nonopportunistic infections,[15] again obviously based on HIV-induced immunosuppression.

Arthritis

Arthritis is the typical manifestation of infection with caprine arthritis-encephalitis virus in adult goats (2 to 9 years old), where primarily the carpal joints are affected ("big knee" disease[16]). Sometimes it is seen in sheep infected with maedi and visna viruses.

Mastitis

Mastitis is associated with,[17] but not unequivocally proved to be caused by, caprine arthritis-encephalitis virus. Most cases occur 1 to 3 days after parturition. Recovery is slow, and full milk production is rarely achieved.[16] Udder inflammatory lesions are also seen in some sheep infected with maedi and visna viruses.

Central Nervous System Diseases

Neurologic disorders are the most frequent clinical expression in goats infected with arthritis encephalitis virus up to 6 months of age.[18] The typical clinical symptoms are ataxia and lameness. Central nervous system disturbances are an infrequent complication of visna virus infection. Subacute encephalitis (with ataxia) has also been described in horses after equine infectious anemia virus infection. Neurologic disorders are frequently seen in HIV infection.[19] Furthermore, some reports link certain human neural diseases, e.g., tropical spastic paraparesis, to HTLV-I infections,[20] although actual data suggest tropical spastic paraparesis to be caused by viruses related to HTLV-I but with distinct biological differences.[21]

Structure and Replication of Retroviruses

All retroviruses have a central core containing their RNA genome complexed to the enzyme reverse transcriptase. The outer envelope is composed of a lipid-containing membrane with virus-encoded glycoproteins. These glycoproteins are responsible for the attachment to cellular receptors and contain the epitopes for virus neutralization.

The genomic structure of most retroviruses is similar. Retroviruses possess two strands of genomic RNA. Each RNA genome contains three coding genes, namely *gag* for group-specific (core) antigen, *pol* for synthesis of virion-associated RNA-directed DNA polymerase, and *env* for the synthesis of envelope glycoproteins. Unlike all other animal type C retroviruses, all human retroviruses possess a transacting gene, called *tat* (tat-1, tat-2, and tat-3 corresponding to HTLV-I, HTLV-II, and HIV-I). The tat gene encodes a regulatory protein which in turn leads to an abundant virus production. The tat-1 and tat-2 are located at the 3′-terminus of the retrovirus genome, and their protein acts at the transcriptional level via long terminal repeat sequences. The tat-3 gene, however, is located in the middle of the viral genome, and its protein effects post-transcriptional processes.[22] In addition to the tat gene, HIV-I possesses three other genes termed *SOR* (short open reading frame), *3′ORF* (3′ open reading frame) and *art* (antirepression of translation) or *trs* (transregulator of splicing). Art/trs are required for the regulation of HIV expression and replication.[23] The SOR gene is necessary for an effective virus transmission at least in vitro,[24] whereas the role of 3′ORF is not yet fully understood. It should be mentioned here that recently a standard nomenclature was proposed for all known genes of HIV and HTLV.[25]

During the replication of retrovirus, the single-stranded virion RNA is converted into complementary double-stranded virion DNA. During this process, two identical long terminal repeats are formed at each terminus. These long terminal repeats are essential for the integration of the viral DNA into the cellular genome after circularization. Moreover, they contain important regulatory elements for viral replication and are involved in carcinogenesis. The integrated DNA is called provirus.

Relationship Between Human and Animal Retroviruses

There has been a continuous worldwide spread of AIDS since 1981, but the source of its etiologic agent HIV-I is still unknown and the phylogenetic history remains difficult to reconstruct.[26] It has been speculated that HIV might originate from an endemic area in Central Africa or was transmitted from primates to humans by biting and has been adapted as a pathogen since then. These speculations are difficult to confirm by experiments. However, HIV may have been engineered experimentally via recombination—by chance or by intention—using the genetic material of different human and animal retroviruses. Possible animal virus candidates for such a recombination could be maedi, visna, and equine infectious anemia viruses and a feline lentivirus described recently.[6] A recent study compared the published nucleotide sequences of several human and animal retroviruses.[27] The results conclusively demonstrated that the sequence homology between HIV and visna virus is too little to consider animal lentiviruses as recent ancestors of HIV. A similar conclusion was drawn for HTLV-I. Gonda et al[28] demonstrated by heteroduplex analysis that the percentage of genome homology between HIV and animal lentiviruses was about 35% under low stringency or 15% under high stringency conditions. Thus, all published data confirm a genetic relationship between HIV and animal lentiviruses but disprove their identity. Therefore, the origin of HIV remains unknown at present.

Mechanism of Retrovirus-Induced Carcinogenesis

Tumors are caused by members of the Oncovirinae subfamily. All proviruses possess at least the three genes, gag-pol-env. Some, however, harbor additional information, which is important for the pathogenesis of these agents. Rous sarcoma virus, for instance, possesses a viral oncogene (v-onc), called v-src. This means, simply spoken, that expression of this gene leads to transformation of the infected cell. It is an acutely transforming virus. Into this category also belong other sarcoma viruses (e.g., feline and avian sarcoma viruses). Besides an intact oncogene, they contain a merely truncated genome, which means they depend on helper viruses for their replication.

Bovine leukemia virus and HTLV possess no v-onc, but a so-called tat gene (transacting transcription), as already mentioned, whose expression leads to an increased replication of the virus by acting on the long terminal repeats.

How do these viruses cause cancer? In the case of viruses containing a v-onc, this is readily conceivable. They harbor the information for the transforming protein in their genome and transfer it into the cell, where it is expressed (this is called transduction). The discovery of viral oncogenes has led to the surprising detection that each animal or human genome examined contained oncogenes (c-onc or proto-onc), which differ only slightly from v-onc.[29] Presumably, they are necessary for the normal ontogenesis of the individual. In differentiated cells, they are "silent." By integration in the neighborhood of c-onc genes, however, retroviruses are able to activate these oncogenes, leading to an overexpression of these host genes. This process is enabled by their long terminal repeat structures, which contain, as mentioned, regulatory sequences (e.g., promotors).

Since retroviruses possess identical long terminal repeats at each terminus, this regulation can also influence the transcription of cellular genomes. Furthermore, some long terminal repeats contain so-called enhancers (sequences that amplify transcription of the viral genome), which may act on cellular DNA even after inverted integration. A prerequisite for this mechanism (called insertional mutagenesis), however, is the specific integration in the neighborhood of a c-onc. This may, at least in part, explain the rare frequency of tumors after infection with retroviruses lacking such v-onc genes.

In the case of the group comprising bovine leukemia virus, HTLV-I, and HTLV-II, it has been discussed whether expression of the tat gene not only upregulates viral replication, but also transactivates a cellular gene. Therefore, no specific integration would be necessary. It has been shown that HTLV-I could induce cellular gene activity, viz., interleukin-2 production and receptor expression in resting T lymphocytes.[30] Furthermore, recent data confirm that the tat gene product of HTLV-I may be regarded as an oncogenic protein, since it could induce mesenchymal tumors in transgenic mice.[31]

The oncogene products, as the transforming principle, can be classified into several categories with respect to their biochemical and functional properties,[32] but a discussion is beyond the scope of this review.

Besides these direct effects, indirect mechanisms, such as chronic immune suppression, long-term immune stimulation, or growth factor release, may act as supporting factors in leukemogenesis. One has to keep in mind, however, that the preceding description surely is a simplification, since transformation is a multistep event.[33]

Pathogenetic Mechanisms of Lentiviral Infection

Keeping in mind the diversity of clinical pictures caused by lentiviruses, it is not surprising that there is no single common pathogenic mechanism. Some motifs, taken together, give some insight into the pathogenesis of these infections.

The main question in lentiviral pathogenesis concerns why the virus persists, even in the face of a vigorous immune response of the infected host?

One important mechanism is the establishment of a latent state. Latency is an important feature of all retroviruses. In an integrated, latent state without expression, the virus can escape the immune surveillance. This may also contribute to the long incubation period. All important lentiviruses are able to integrate. It is discussed, however, whether extrachromosomal DNA forms, found in maedi and visna viruses as well as HIV-infected cells, may play a role for the cytopathogenicity of these viruses, which is uncommon for retroviruses. Viruses can be reactivated from this latent state, for example, by cell differentiation from monocyte to macrophage in the case of maedi, visna, and caprine arthritis-encephalitis viruses.[34] In the case of HIV, activation of the lymphocyte harboring the provirus seems to be necessary for viral replication. This may be achieved by mitogens, activation by macrophages, or other infections accompanying HIV infection. Cytokines obviously play an important role.[35]

The main characteristic of lentivirus infection at the molecular level probably is restricted gene expression.[36] This has particularly been studied for maedi and visna virus infection. It may, at least in part, also explain the silent and insidious nature of the disease, with apparent infection being rare, although subclinical effects may arise. In contrast, in tissue culture maedi and visna virus replicates in a lytic and highly productive cycle. In vivo, gene expression is restricted in most infected cells. A few cells, however, have relatively high RNA levels, and antigen is detectable. This is correlated with the grade of inflammatory response and tissue damage. This means that low level gene expression serves as a continuous inflammatory stimulus (because the host cannot eliminate the virus) and determines form and temporal course of pathology. Thus, visna virus RNA and antigen could be detected in glial cells in foci of demyelination of the infected sheep brain.[37] Analogous immune mechanisms have been discussed for arthritis induced in goats.[38]

It is not fully understood which factor(s) account for this gene restriction. There may be some intracellular factors involved which could be based on the complex control of viral transcription/translation, e.g., by transacting proteins.[39] Furthermore, interferon-mediated effects have been discussed (see below).

In the natural disease, maedi, visna, and caprine arthritis-encephalitis viruses infect macrophage precursors (monocytes) and persist there in a latent state. This may be important for the dissemination of the virus beyond the initial infection, and on the other hand may allow the virus to avoid detection and elimination by effector cells. Reactivation and virus replication occur at a modest level during maturation of the precursor monocyte to macrophages, as mentioned above. Infected precursors in the bone marrow are thought to serve as a virus reservoir.[40]

Virus replication in macrophages in different locations results in lesions, characterized by mononuclear cell infiltration of the central nervous system, lungs, synovium, mammary glands, and their draining lymph nodes. In vitro, caprine arthritis-encephalitis virus can increase macrophage division.[41] Infected macrophages may transfer virus into the brain (choroid plexus), thereby displaying a "Trojan horse" mechanism.[42] Furthermore, they are thought to be vehicles for the transmission of the disease via colostrum. Macrophages infected by maedi, visna, and caprine arthritis encephalitis viruses induce a unique interferon production,[43] but only in the presence of T lymphocytes. This is unusual, because in general the infected cell itself produces interferon. Presumably, the macrophage releases a substance which serves as a signal for the lymphocyte to secrete lentivirus interferon. Zink et al[44] suggest that this interferon functions in retarding the rate of maturation of monocytes, thus reducing the permissiveness of virus production. It furthermore restricts the rate of virus replication in mature macrophages. Not unusual for interferon, it also enhances expression of class II major histocompatibility antigens. This enables interaction with T-helper/inducer cells (antigen presentation), thus augmenting the host's lymphoproliferative response to the virus. It also amplifies the local immune response by attracting reactive cells. All these mechanisms, however, obviously are not sufficient to terminate the infection and thus may favor virus persistence and harm the host.

Equine infectious anemia virus obviously infects and replicates in mature macrophages.[45] Only selective populations are infected such as the Kupffer cells of the liver causing liver diseases. The lungs, however, are not affected by the equine infectious anemia virus in contrast to the maedi and visna viruses.

Some controversy exists about the role of macrophage infection in human AIDS. It is now known that HIV does not exclusively infect T-helper/inducer cells but, among others, also macrophages. Some authors even claim that they may be the primary target cell.[46] Gartner et al[47] discerned evidence for preferential tropism of brain and lung HIV-I isolates for macrophage infection. In humans showing encephalopathy, the mononuclear cells in the brain harbor the virus. They are thought to originate from the peripheral blood, which may serve as a reservoir, and traverse the blood-brain barrier (as seen with the maedi and visna viruses). Infected macrophages may secrete factors that cause extensive tissue injury and edema. Alternatively, the expression of viral antigen on the surface may elicit a delayed-type hypersensitivity. Mononuclear cells harboring the virus have also been isolated from lung tissue of positive patients. Macrophages are not destroyed by HIV replication, thus serving as a reservoir which might be pivotal in the pathogenesis of human AIDS.[48] There are some hints that after their activation macrophages interact with T-helper cells, the preferential target of HIV, thus leading to a secondary infection.

Another important question is whether lentivirus infections induce neutralizing antibodies. In goats infected with the arthritis-encephalitis virus, neutralizing antibodies are lacking. One explanation could be that the immune system is deficient for this specific antigen. Another possibility is the lack of appropriate quantitative or qualitative epitopes (e.g., glycoproteins). Most interestingly, goats could develop neutralizing antibodies after immunization with inactivated *Mycobacterium tuberculosis*, indicating that this lack is due to an hyporesponsive state of the animal.[49] Recent data[50] show that caprine arthritis-encephalitis virus is heavily sialylated. Removal of sialic acids enhanced the kinetics of neutralization of the virus by goat antibodies. This suggests that carbohydrates on the viral surface could protect the virus from rapid neutralization by antibodies.

In contrast to caprine arthritis encephalitis virus infection, sheep infected with maedi and visna viruses develop neutralizing antibodies, but obviously they are not able to abolish the infection. There are some reasons for this failure. One is the latent state (integration) of maedi and visna viruses, which cannot be recognized by antibodies. Another may be the antigenic instability of the virus. Furthermore, the virus can spread from cell-to-cell and thus is unattainable for neutralizing antibodies. Moreover, recent in vitro studies have shown that the kinetics of binding of the antibodies to the virus were much slower than the binding of the virus to the target cell, the macrophage.[51] Therefore, persistent virus infection in sheep may be facilitated by virus spread from macrophage to macrophage before efficient neutralization can occur.

As in the case of equine infectious anemia virus, neutralizing antibodies directed against the envelope proteins exist, but have only a temporary effect because of the emergence of new variants with altered glycoprotein structures ("antigenic drift"). Furthermore, recent studies after experimental infection with equine infectious anemia virus revealed that only moderate levels of neutralizing antibodies were present compared to large amounts of antiglycoprotein antibodies, thus indicating that most immunogenic sites on the viral surface are not sensitive to neutralization.[52] Using monoclonal antibodies, Hussain et al[53] identified a neutralizing domain on the surface glycoprotein gp90.

In the case of HIV infection, apparently conflicting results regarding neutralizing antibodies exist. Whenever they were described, they were only present in very low concentrations.[54] The reasons may be antigenic variability or cell-to-cell spread as described for maedi and visna viruses. Furthermore, an inaccessibility of antibodies to critical epitopes is discussed, due to the heavy glycosilation of the envelope proteins. This would suggest that neutralizing antibody is prevented from binding to the viral epitope by masking carbohydrate chains. Another feature of the HIV infection, the so-called antigen shedding,[55] a release of a considerable amount of the envelope protein gp 120 from the infected cell and the mature virion as well, containing important epitopes, could be involved by capturing neutralizing antibodies, which consequently are not available for neutralizing the virus.

Antigenic variation represents an additional mechanism for the persistence and spread of leukemia viruses. The underlying mechanism is the emergence of mutants with altered envelope glycoproteins against which neutralizing antibodies are directed, thus enabling this virus subpopulation to escape the immunologic inactivation.

For equine infectious anemia viruses, this mechanism is of great importance for the course of the disease and dissemination of the virus. During each cycle of virus replication, the virus isolated is refractory to neutralization by antibody that neutralized previous isolates. This is probably due to an accumulation of point mutations in the env-gene.[56] Such mutations are presumed to alter the interaction of the surface glycoproteins with the neutralizing antibodies (antigenic drift). The replication of the new variant, however, elicits new neutralizing antibodies, and replication ceases. But new variants arise by this selection pressure, which are not inactivated by the latter neutralizing antibodies and so on. On the other hand, Carpenter et al[57] presented data after experimental infection of horses with equine infectious anemia virus that multiple clinical cycles could occur before neutralizing antibodies were detectable. But interestingly, those early immune sera could antigenically distinguish the different virus isolates. This would suggest that antigenic variation is due to an immune recognition and destruction of virus-infected cells rather than to the selective pressure of specific antibodies.

There is some controversy about the importance of antigenic variation for the pathogenesis of the maedi and visna viruses. Antigenically distinct viruses could be isolated after experimental infection and long-term observation at considerable frequency. But there are data[58] showing that emerging visna virus variants did not replace the inoculum strain (in contrast to equine infectious anemia virus), so that antigenic variation may play a minor role in maedi-visna virus infection. Antigenic variation during persistent infection with caprine arthritis-encephalitis virus has been demonstrated by Ellis et al.[59] Here, too, the variant virus and the inoculum virus were shown to coexist in the infected animal.

The HIV isolates may also markedly differ in their env-proteins.[60] Again, one individual can harbor several HIV isolates simultaneously.

Immunosuppression is an additional factor which facilitates virus persistence. Many oncogenic viruses and especially infections with HIV are associated with a decline in immunocompetence after infection. In the Oncornavirinae subfamily, immunosuppression is the most frequent and devastating effect of feline leukemia virus infection.

One effect of immunosuppression induced by feline leukemia virus may result from replication of the virus in lymphoid tissues and bone marrow, which may depress normal cell turnover and initiate atrophy. On the other hand, it has been shown, that the application of killed virus for vaccine experiments causes immunosuppression, too. Subsequent experiments have shown that an envelope protein, called p15E, among other effects was able to suppress mitogen-induced lymphocyte proliferation.[61] This may be due by eliminating secretion and action of interleukin 2. It is very interesting that regions of this p15E protein are conserved among retroviruses such as murine and feline leukemia viruses, HTLV-I, HTLV-II, and HIV. A peptide, homologous to this conserved region, could inhibit human natural killer cell activity in vitro.[62]

Some authors claim, however, that the immunosuppressive properties of feline leukemia virus infection are attributed to replication-defective mutants, arising during the natural course of infection with replication-competent feline leukemia virus.[63,64] Furthermore, as already mentioned above, a similar or identical lentivirus has been isolated from immunocompromised cats.[5,6]

The central event in the immunopathogenesis of AIDS is the selective depletion of a T-cell subset, called T4 helper-inducer cell, which expresses the CD4 antigen on the cell membrane. Besides its physiologic role, it serves as an HIV receptor.[65] The T4 cell has the major responsibility for orchestrating virtually all immune functions, e.g., cytotoxic and suppressor activities, immune globulin production, and lymphoid factor secretion. One way the T4 cell can be eliminated is its destruction by (cytopathic) HIV, which presumably does not occur until activation of the lymphocyte. But only one in 10,000 to 100,000 T4 cells harbors the virus, so there must be additional, indirect mechanisms of T4 cell depletion.

There are some theories and speculations about such effects. Infected T4 cells express the glycoprotein gp120 on their surface. This is recognized by uninfected T4 cells, which possess the receptor (CD4) for this protein. After binding to the infected cell, a presumably gp120-driven cell fusion may take place resulting in multinucleated giant cells (syncytia), which cannot survive.[66]

Another possibility discussed is the destruction of infected T4 cell by cytotoxic T cells, which recognize the viral antigen on the lymphocyte (autoimmune reaction). Because of the antigen shedding, even noninfected T4 lymphocytes may bear this protein on their surface bound on their CD4 receptor. In addition to preventing their functioning as helper cells, these cells, too, may be killed (erroneously) by cytotoxic T cells. Humoral complement-mediated cytotoxic mechanisms, however, have also been described.[67] Furthermore, soluble factors are conceivable, which are toxic or at least immunosuppressive for T4 cells. The gp41, the homologous protein of p15E, would be a candidate.

Persistent other active viral infections, often associated with AIDS, such as with Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and hepatitis B virus may moreover contribute to the immune pathogenesis, leading to a vicious cycle of infection and immune deficiency enhancing each other.

Autoimmune phenomena are seen in infection by equine infectious anemia virus. The typical anemia is a result of a reduced lifespan of erythrocytes as well as decreased erythropoiesis.[11] The first is due to an autoimmune reaction. Viral hemagglutinin subunits are fixed to erythrocytes and subsequently bind antibodies and complement, resulting in an immune-mediated hemolysis, followed by erythrophagocytosis by activated macrophages. The depressed erythropoiesis may be a result of changes in iron metabolism.

Autoimmune phenomena are also seen in human AIDS. Furthermore, in sera of HIV patients, increased titers of natural autoantibodies and antilymphocyte antibodies could be detected.[68]

Conclusion

From the precedent can be deduced that an infection of the cell by a retrovirus has two principal consequences—the cell may become transformed (a proliferative-productive event) or it will be altered irreversibly and destroyed (a destructive-degenerative process). A good example for this inherent ambivalence is the infection of the T4 helper/inducer cell with HTLV-I, leading to an uncontrolled proliferation, whereas the same cell when infected with HIV will be lysed.

Altogether, the retroviruses present themselves as a heterogeneous family. It is now evident that some morphological characteristics and many pathogenic and biological features of retroviruses cross subfamily classifications.[69] HTLV, for instance, may cause tumors, but there is now evidence for its etiology in nerve diseases, too. Such neurologic disorders have been thought up to now to be a domain of lentiviruses. Feline leukemia virus is oncogenic, but also provokes severe immunosuppression, which is similar to that seen after HIV infection. The latter, however, is often associated with tumors and so on.

These blurring differences are also evident at the genomic level, so HTLV and bovine leukemia virus possess an RNA organization reminiscent of lentiviruses.

A lot of questions remain unanswered. A positive prospect is, however, that now the tools for investigating the molecular pathogenesis are available, and human and veterinary virology may act together to gain more knowledge about these viruses, which may be fruitful for both humans and animals.

A negative prospect is that the features described, e.g., latent infection, antigenic variation, insufficient neutralization, and autoimmune reactions, are obstacles in the development of prophylactic measures (vaccination), representing a challenge for the years to come.

References

1. Ford RB. Feline leukemia virus: the infection. PM Vet Hosp 1985;1:1-7.
2. Wong-Staal S, Gallo RC. Human T-lympotropic retroviruses. Nature 1985;317:395-403.
3. Burny A, Bruck C. Cleuter Y, et al. Bovine leukemia virus and enzootic bovine leukosis. Onderstepoort J Vet Res 1985;52:133-44.
4. Ziegler JL. AIDS and cancer. Ann Inst Pasteur/Immunol 1987;138:253-60.
5. Pedersen NC, Ho EW, Brown ML, Yamamoto JK. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. Science 1987;235:790-3.

6. Harbour DA, Williams PD, Gruffydd TJ, et al. Isolation of a T-lymphotropic lentivirus from a persistently leucopenic domestic cat. Vet Rec 1988;122:84-6.
7. Ungar-Waron H, Trainin Z. Immunological aspects of enzootic bovine leukemia. In: Burny A, Mammerickx M, eds. Enzootic bovine leukosis and bovine leukemia virus. Boston: Martinus Nijhoff Publishing, 1987:163-73.
8. Takamatsu H, Inumaru S, Nakajima H. Inhibition of in vitro immunocyte function by sera from cattle with bovine leukosis. Vet Immunol Immunopathol 1988;18:349-59.
9. Gonda MA, Braun MJ, Carter SC, et al. Characterization and molecular cloning of a bovine lentivirus related to human immunodeficiency virus. Nature 1987;330:388-91.
10. Wellman ML, Kociba GJ, Lewis MG. Inhibition of erythroid colony-forming cells by a Mr 15,000 protein of feline leukemia virus. Cancer Res 1984;44:1527-9.
11. Cheevers WP, McGuire TC. Equine infectious anemia virus: immunopathogenesis and persistence. Rev Infect Dis 1985;7:83-8.
12. Roberts DH, Lucas M. Equine infectious anaemia. Vet Annual 1987;147-50.
13. Ellis TM, Robinson WF, Wilcox GE. The pathology and aetiology of lung lesions in goats infected with caprine arthritis-encephalitis virus. Aust Vet J 1988;65:69-73.
14. Cutlip RC, Jackson TA, Lehmkuhl HD. Lesions of ovine progressive pneumonia: interstital pneumonitis and encephalitis. Am J Vet Res 1979;40:1370-4.
15. Milar A. AIDS and the lung. Br Med J 1987;294:1334-7.
16. Robinson WF, Ellis TM. Caprine arthritis-encephalitis virus infection: from recognition to eradication. Aust Vet J 1986;63:237-41.
17. Kennedy-Stoskopf S, Narayan O, Strandberg JD. The mammary gland as a target organ for infection with caprine arthritis-encephalitis virus. J Comp Pathol 1985;95:609-17.
18. Narayan O, Cork LC. Lentiviral diseases of sheep and goats: chronic pneumonia, leukoencephalomyelitis and arthritis. Rev Infect Dis 1985;7:89-98.
19. Barnes DM. Brain damage by AIDS under active study. Science 1987;235:1574-7.
20. Marx JL. Leukemia virus linked to nerve disease. Science 1987;236:1059-61.
21. Jacobson S, Raine CS, Mingioli ES, McFarlin DE. Isolation of an HTLV-I-like retrovirus from patients with tropical spastic paraparesis. Nature 1988;331:540-3.
22. Chen ISY. Regulation of AIDS-virus-expression. Cell 1987;47:1-2.
23. Feinberg MB, Jarrett RF, Aldovini A, et al. HTLV-III expression and production involve complex regulation at the levels of splicing and translation of viral RNA. Cell 1986;46:807-17.
24. Fisher AG, Ensoli B, Ivanoff L, et al. The sor gene is required for efficient virus transmission in vitro. Science 1987;237:888-93.
25. Gallo R, Wong-Staal F, Montagnier L, et al. HIV/HTLV gene nomenclature. Nature 1988;333:504.
26. Smith TF, Srinivasan A, Schochetman G, et al. The phylogenetic history of immunodeficiency viruses. Nature 1988;333:573-5.
27. Modrow S, Hahn BH, Shaw GM, et al. Computer-assisted analysis of envelope protein sequences of seven human immunodeficiency virus isolates: prediction of antigenic epitopes in conserved and variable regions. J Virol 1987;61:570-8.
28. Gonda MA, Braun MJ, Clements JE, et al. Human T-cell lymphotropic virus type III shares sequence homology with a family of pathogenic lentiviruses. Proc Natl Acad Sci USA 1986;83:4007-11.
29. Bishop MJ. Cellular oncogenes and retroviruses. Ann Rev Biochem 1983;52:301-54.
30. Gazzolo L, Dodon MD. Direct activation of resting T lymphocytes by human T-lymphotropic virus type I. Nature 1987;326:714-7.
31. Nerenberg M, Hinrichs SH, Reynolds RK, et al. The tat gene of human T lymphotropic virus type I induces mesenchymal tumors in transgenic mice. Science 1987;237:1324-9.
32. Nishimura S, Sekiya T. Human cancer and cellular oncogenes. Biochem J 1987;243:313-27.
33. Neil JC, Forrest D. Mechanism of retrovirus-induced leukemia: selected aspects. Biochim Biopys Acta 1987;907:71-97.
34. Gendelman HE, Narayan O, Kennedy-Stoskopf S, et al. Tropism of sheep lentiviruses for monocytes: susceptibility to infection and virus gene expression increase during maturation of monocytes to macrophages. J Virol 1986;58:67-74.
35. Fauci AS. AIDS-pathogenic mechanisms and research strategy. ASM News 1987;53:263-6.
36. Haase AT. Pathogenesis of lentivirus infections. Nature 1986;322:130-6.
37. Stowring L, Haase AT, Petursson G, et al. Detection of visna virus antigen and RNA in glial cells in foci of demyelination. Virology 1985;141:311-8.
38. McGuire TC. The immune response to viral antigens as a determinant of arthritis in caprine arthritis-encephalitis virus infection. Vet Immunol Immunopathol 1987;17:465-70.
39. Vigne R, Querat G, Mazarin V, et al. Transcription of visna virus during its lytic cycle: evidence for a sequential early and late gene expression. Virology 1987;161:218-27.
40. Gendelman HE, Narayan O, Molineaux S, et al. Slow, persistent replication of lentiviruses: role of tissue macrophages and macrophage precursors in bone marrow. Proc Natl Acad Sci USA 1985;82:7086-90.
41. Jutila MA, Banks KL. Increased macrophage division associated with infection by caprine arthritis encephalitis virus. Fed Proc 1986;45:4647.
42. Peluso R, Haase A, Stowring L, et al. A Trojan horse mechanism for the spread of visna virus in monocytes. Virology 1985;147:231-6.
43. Denman AM. Induction of interferon by lentiviruses. Immunol Today 1986;7:201-2.
44. Zink MC, Narayan O, Kennedy PGE, Clements JE. Pathogenesis of visna/maedi and caprine arthritis-encephalitis: new leads on the mechanism of restricted virus replication and persistent inflammation. Vet Immunol Immunopathol 1987;15:167-80.
45. Clements JE. Hypothesis on the molecular basis of nononcogenic retroviral diseases. Rev Infect Dis 1985;7:83-8.
46. Popovich M, Read-Connole E, Gartner S. Biological properties of HTLV-III/LAV: a possible pathway of natural infection in vivo. Ann Inst Pasteur/Immunol 1986;137:413-7.
47. Gartner S, Markovits P, Markovitz DM, et al. The role of mononuclear phagocytes in HTLV III/LAV infection. Science 1986;233:215-9.

48. Pauza CD. HIV persistence in monocytes leads to pathogenesis and AIDS. Cell Immunol 1988;112:414-24.
49. Narayan O, Sheffer D, Griffin DE, et al. Lack of neutralizing antibodies to caprine arthritis-encephalitis lentivirus in persistently infected goats can be overcome by immunization with inactivated Mycobacterium tuberculosis. J Virol 1984;49:349-55.
50. Huso DL, Narayan O, Hart GW. Sialic acids on the surface of caprine arthritis-encephalitis virus define the biological properties of the virus. J Virol 1988;62:1974-80.
51. Kennedy-Stoskopf S, Narayan O, Strandberg JD. Neutralizing antibodies to visna lentivirus: mechanism of action and possible role in virus persistence. J Virol 1986;59:37-44.
52. O'Rourke K, Perryman LE, McGuire TC. Antiviral, antiglycoprotein and neutralizing antibodies in foals with equine infectious anemia virus. J Gen Virol 1988;69:667-74.
53. Hussain KA, Issel CJ, Schnorr KL, et al. Antigenic mapping of the envelope protein of equine infectious anemia virus: identification of a neutralizing domain and a conserved region of glycoprotein 90. Arch Virol 1988;98:213-24.
54. Klatzman D, Gluckman JC. HIV infection: facts and hypotheses. Immunol Today 1986;7:291-6.
55. Schneider J, Kaaden OR, Copeland TD, et al. Shedding and interspecies type sero-reactivity of the envelope glycopolypeptide gp120 of the human immunodeficiency virus. J Gen Virol 1986;67:2533-8.
56. Salinovich O, Payne SL, Montelaro RC, et al. Rapid emergence of novel antigenic and genetic variants of equine infectious anemia virus during persistent infection. J Virol 1986;57:71-80.
57. Carpenter S, Evans LH, Sevoian M, Chesebrow B. Role of the host immune response in selection of equine infectious anemia virus variants. J Virol 1987;61:3783-9.
58. Lutley R, Petursson G, Palsson PA, et al. Antigenic drift in visna: virus variation during long-term infection of Iceland sheep. J Gen Virol 1983;64:1433-40.
59. Ellis TM, Wilcox GE, Robinson WF. Antigenic variation of caprine arthritis-encephalitis virus during persistent infection of goats. J Gen Virol 1987;68:3145-52.
60. Coffin JM. Genetic variation in AIDS viruses. Cell 1986;46:1-4.
61. Olsen RG, Mathes LE, Tarr MJ, Blakeslee JR. Oncogenic viruses of domestic animals. Small Animal Pract 1986;16:1129-44.
62. Harris DT, Cianciolo GJ, Synderman R, et al. Inhibition of human natural killer cell activity by a synthetic peptide homologous to a conserved region in the retroviral protein p15E. J Immunol 1987;138:889-94.
63. Mullins JI, Chen CS, Hoover EA. Disease-specific and tissue-specific production of unintegrated feline leukemia virus variant in feline AIDS. Nature 1986;319:333-6.
64. Overbaugh J, Donahue PR, Quackenbush SL, et al. Molecular cloning of a feline leukemia virus that induces fatal immunodeficiency disease in cats. Science 1987;239:906-10.
65. Sattentau QJ, Weiss RA. The CD4 antigen: physiological ligaud and HIV receptor. Cell 1988;52:631-3.
66. Lifson JD, Feinberg MB, Reyes GR, et al. Induction of CD4-dependent cell fusion by the HTLV-III/LAV envelope glycoprotein. Nature 1986;323:725-8.
67. Stricker RB, McHugh TM, Moody DJ, et al. An AIDS-related cytotoxic autoantibody reacts with a specific antigen on stimulated CD4 T cells. Nature 1987;327:710-3.
68. Matsiotá P, Chamaret S, Montagnier L, Avrameas S. Detection of natural autoantibodies in the serum of anti-HIV-positive individuals. Ann Inst Pasteur/Immunol 1987;138:223-33.
69. Levy JA. The multifaceted retrovirus. Cancer Res 1986;46:5457-68.

Case Reports

MITRAL VALVE PROLAPSE WITH SYSTEMIC EMBOLISM: REPORT OF THREE CASES

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Mitral valve prolapse (MVP) is a common condition in the developed countries and apparently is the most frequently diagnosed valvular heart disease in the United States, with an overall prevalence of 5% and as high as 17% in young females.[1] Several clinical studies have suggested that MVP is associated with certain serious complications such as progressive mitral regurgitation, bacterial endocarditis, arrhythmias, and sudden death.[2] Moreover, cerebral and ophthalmic ischemic episodes, presumably secondary to embolism, have been reported recently as additional complications of MVP.[3-13]

It is generally believed that rheumatic fever is still a major problem in the developing countries.[14] Thus, it is assumed that the commonest form of valvular heart disease in these areas is rheumatic in origin. A recent study has shown that the prevalence rate for MVP in Saudi Arabia is comparable to that reported from the Western countries.[15] There should be an awareness of its occurrence and possible complications in the developing countries.

We, therefore, present case reports of three young Saudis with MVP complicated by cerebral and retinal embolism and review the relevant literature. Similar complications have been reported previously only from Canada,[3-5] England,[6] South Africa,[7] France,[8] and the United States,[9-13] but to our knowledge, these are the first cases reported from the Middle East and Asia of cerebral and retinal embolic phenomena associated with MVP.

Case Reports

Case 1

A 16-year-old Saudi girl was referred to the University Hospital because of sudden blindness in the right eye which developed about 12 hours prior to presentation. There was no history of acute rheumatic fever, heart disease, dyspnea, chest pain, palpitations, dizziness, or previous visual symptoms. Ophthalmic examination revealed blindness of the right eye with only perception to light. Features of right central retinal artery occlusion were seen on funduscopy. Carotid pulses were normal, and there was no carotid artery bruit. She was afebrile, and the cardiac apex was in the normal location with no thrill or heaves. First and second heart sounds were normal. There was a grade 3/6 late systolic murmur at the apex, which was accentuated by hand grip. No click, gallop, or opening snap was heard. Results of all hematologic and biochemical investigations were normal. Blood culture showed no growths. Electrocardiograms and chest roentgenogram were normal. No arrhythmia was observed on a 24-hour Holter monitor recording. Echocardiogram showed holosystolic MVP with normal left atrial and left ventricular size.

Case 2

For a month prior to his referral, a 23-year-old Saudi man experienced recurrent attacks of blurred vision lasting a few minutes at a time. Four days before his visit to the University Hospital, he suddenly developed partial blindness in the midzone of the visual field of the left eye. At presenta-

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tion, he denied any history of rheumatic fever, palpitation, dizziness, chest pain, or dyspnea. Ophthalmic evaluation showed a visual acuity of 0.8 in the left eye and 1.0 in the right eye. Retinal examination revealed obstruction of the left cilioretinal artery with an ischemic area in the retina involving the inferior part of the macula. The carotid pulses were normal with no bruits, while the apical cardiac impulse was in the normal location with no thrills or heaves. First and second heart sounds were normal. There was no click, but an S3 gallop was noted. A grade 1/6 late systolic murmur, which increased to grade 3/6 in the squatting position with a change to musical character, was heard at the mitral area. Results of all hematologic and biochemical investigations were normal. Electrocardiogram and chest roentgenogram were unremarkable. M-mode echocardiography showed thickened posterior leaflet but no evidence of prolapse of the mitral valve. However, the apical four-chamber view on two-dimensional echocardiography showed definite MVP (Figure 1). The left atrial and left ventricular chamber sizes were normal.

Case 3

This 21-year-old Saudi man was admitted to the neurosurgical unit of the University Hospital with the chief complaint of frontal headache, loss of recent memory, and olfactory hallucination (strange odors) for 1 day prior to admission. At that time, his mother, while riding with him in the car, noticed that his behavior was abnormal and that he lost his way while driving to a familiar place. She also observed that his conversation did not make sense. On the morning of admission, he woke up complaining of frontal headache and smelling strange odors. Later that day, the rest of his family realized that he could not remember most of the events of the previous 2 weeks. There was no history of trauma or any other illness in the past. General examination revealed a slightly drowsy but fit-looking young man. Neurologic examination was unremarkable except for evidence of loss of recent memory. Carotid pulses felt equal on palpation, and no bruits were heard. The apical cardiac impulse was not displaced. First and second heart sounds were normal. A midsystolic click and a grade 3/6 late systolic murmur were heard at the apex. These signs were interpreted as indicative of MVP. Results of all hematologic and biochemical investigations were normal.

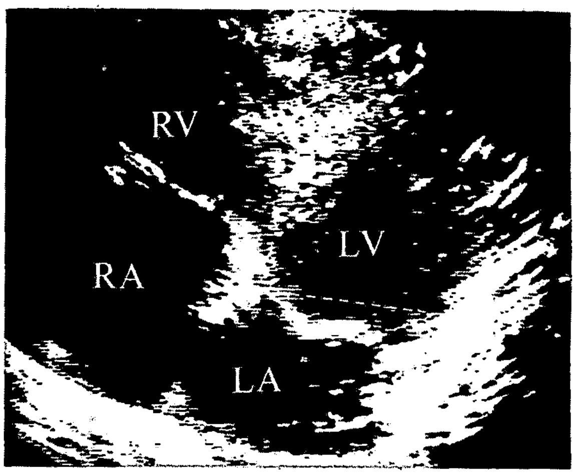

FIGURE 1. Two-dimensional echocardiogram (four-chamber apical view) clearly shows both leaflets of the mitral valve prolapsing well into the left atrium during systole. The dotted line defines the mitral annular plane. LV indicates left ventricle; LA, left atrium; RV, right ventricle; and RA, right atrium.

Computed tomographic scan of the brain showed an area of low density in the right temporal region with no enhancement with contrast (Figure 2). The EEG showed irregular slow and sharp waves in the right hemisphere with the maximum voltage in the anterior to mid-temporal region, suggesting an irritative lesion which may have caused a focal seizure. No arrhythmia was recorded in 24-hour Holter monitoring. Echocardiogram showed holosystolic MVP with normal left atrial and left ventricular size.

Discussion

In 1966 Barlow and Bosman described a 23-year-old woman with MVP who experienced transient left arm weakness, but they did not relate the neurologic disorder to her cardiac lesion.[16] In 1976 Barnett et al were the first to suggest an association between cerebral ischemic events and MVP and proposed that the ischemic episodes were thromboembolic in origin.[3] On the other hand, the earliest report of retinal vascular lesions in MVP was presented by Woldoff et al.[11] Since then, there have been numerous communications suggesting a causal relationship between MVP and ischemia of the eye and brain.[3-13] None of our three patients with MVP suffered from

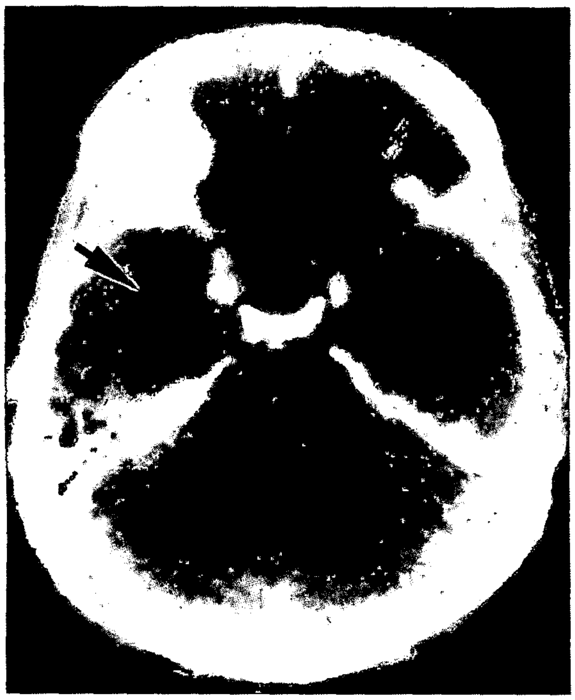

FIGURE 2. Skull CT scan shows the low-density area (arrow) in the right temporal lobe.

hypertension, diabetes mellitus, rheumatic heart disease, vasculitis, hematologic disorders, or any other predisposing factor for strokes. Therefore, it is very likely that the ischemic attacks in these young Saudis were due to thrombotic emboli originating in a prolapsed mitral valve.

In case 2, only the apical four-chamber view showed the MVP without evidence of prolapse on the M-mode or the parasternal long axis view, though the mitral valve leaflets, especially the posterior, were thickened. Recently, the reliability of the apical four-chamber view for the diagnosis of MVP has been questioned.[17] However, in this patient, both the anterior and posterior leaflets showed marked superior displacement with their coaptation distinctly superior to the mitral annular plane (3+ displacement). This pattern is very unusual in a normal subject.[17,18] Abbasi et al have shown that the four-chamber view was significantly more sensitive than M-mode and long axis for the diagnosis of MVP.[19] If one applies the diagnostic criteria suggested by Perloff et al, this patient has two major (apical systolic murmur and marked superior systolic displacement of the mitral leaflets and their coaptation) and one minor criteria (focal neurologic attack). They believe that one or more major criteria establish the probability of pathologic MVP beyond reasonable doubt.

The observed association of MVP and thromboembolism has generated considerable interest and controversy. The possibility of a coincidental occurrence of two common clinical conditions cannot be entirely ruled out. It is, however, extremely important to determine the relationship between MVP and thromboembolic phenomena so that appropriate preventive action can be taken if the association turns out to be causal in nature. Since arrhythmias are a relatively common complication of this valvular disorder, thromboembolism in MVP may be secondary to atrial fibrillation. Alternatively, embolization may be due to infective endocarditis. Nevertheless, in most cases of MVP, emboli probably arise from either noninfective thrombotic vegetations formed over ulcerative lesions on a valve with myxomatous degeneration[5,7,10,20] or from a thrombus formed in a small cul-de-sac between the left atrial wall and the atrial side of the ballooning mitral leaflet.[4]

Interestingly, Steele and colleagues have suggested that the decreased platelet survival time in their MVP patients was due to the deposition of platelets with formation of platelet thrombi on an abnormal prolapsed mitral valve.[21] Barnett et al, in their original paper, reported 12 cases of MVP with cerebral ischemic events.[3] Three of them suffered from atrial fibrillation. Ten had abnormal physical findings in the form of a click, a murmur, or both. Four had normal echocardiogram although all of them had proved MVP by angiocardiography. Subsequently in another study, this same group of workers found MVP in a significantly higher percentages of subjects among young persons (below 45 years) presenting with strokes compared to age-matched controls.[5] Despite these and other reports, the role of MVP in cerebral ischemia remains controversial for several reasons.

First, there is lack of direct pathologic proof. Because of the relatively young age of the patients and the nonlethal nature of the ischemic brain or eye insult, significant postmortem evidence is lacking. However, there is some indirect evidence in that fibrin and platelet thrombi have been observed at surgery and autopsy on the surface of mitral valve with myxomatous degeneration.[10,22] Although there have been four cases of autopsied fatal embolism reported, in one case there was no thrombus seen in the heart.[23] Two cases had another predisposing factor (one had atrial fibrillation and one had an adenocarcinoma),[24,25] There was only one case with documented thrombus on the atrial surface of the posterior mitral valve leaflet.[6] Second, based on their observations in young stroke patients, this causal relationship between cerebral ischemic attacks and MVP has been postulated mainly by neurologists. On the other hand, cardiologists who see a large population of patients with MVP have not recorded an increased risk of strokes among them. In a large cardiac series of 237 patients with echocardiography-documented MVP followed up for a mean period of 6.2 years and maximum of 10.4 years, 10 developed strokes. Of these 10, eight suffered from other disorders that could have caused their stroke (one infective endocarditis, one left ventricular aneurysm with mural thrombus, and six atrial fibrillation). There were, therefore, only two patients of this very large group whose stroke might be explained on the basis of MVP alone.[26] These data strongly argue against a causal relationship between MVP and ischemic events. However, it is possible that only a small subset of MVP patients are prone to this complication. If this is true, then this subset needs to be defined. Suggested features of such a subset include multiple valvular prolapse[27] and redundancy of mitral leaflets.[26] Confirmation of these and evaluation of other possible features is needed.

Physicians who are not aware of the probable association between MVP and embolism are likely to misdiagnose the embolism as being secondary to rheumatic mitral valve disease, particularly in the absence of echocardiography. Interestingly, the first patient was referred to us as a case of embolism due to rheumatic mitral valve disease. Another patient (unpublished) was also initially diagnosed several years ago at another hospital as having retinal embolism complicating rheumatic heart disease. Recent further evaluation, including echocardiography at our hospital, revealed that she was suffering from a prolapsed mitral valve. We feel strongly that in young patients (below 45 years) with acute cerebral ischemic events of unexplained etiology, MVP should be excluded by careful clinical examination and further evaluation which must include echocardiography. Mitral valve prolapse should be considered also as a possible source of embolism in transient ischemic attacks or strokes in some older patients. However, a causative role for MVP in this category of patients would be much harder to prove as there are more common etiologic and risk factors operating in this age group.

From all the available evidence, it would appear that the risk of thromboembolism in the MVP patient population may be restricted to a small subgroup of individuals that is particularly prone to this complication. Therefore, we do not feel it is justified to warn patients of this risk or to use antiplatelet therapy routinely in MVP. Nevertheless, it would be prudent to treat those patients who have had an ischemic episode with antiplatelet drugs. Moreover, in view of the high incidence of MVP in young females, the use of oral contraceptives should be considered contraindicated in those with documented MVP. Further studies to define the prevalence of MVP and its complications are needed not only in Saudi Arabia but also in other regions of the Middle East. Comparisons can then be made with other areas of the world so that a comprehensive and global picture of this apparently common cardiac disorder and its possible complications may begin to emerge.

References

1. Savage DD, Garrison RJ, Devereux RB, et al. Mitral valve prolapse in the general population: I. Epidemiologic features: the Framingham study. Am Heart J 1983;106(3):571-6.
2. Retchin SM, Fletcher RH, Earp J, et al. Mitral valve prolapse: disease or illness? Arch Intern Med 1986;146(6):1081-4.
3. Barnett HJ, Jones MW, Boughner DR, et al. Cerebral ischemic events associated with prolapsing mitral valve. Arch Neurol 1976;33(11):777-82.
4. Kostuk WJ, Boughner DR, Barnett HJ, et al. Strokes: a complication of mitral-leaflet prolapse? Lancet 1977;2(8033):313-6.
5. Barnett HJ, Boughner DR, Taylor W, et al. Further evidence relating mitral-valve prolapse to cerebral ischemic events. N Engl J Med 1980;302(3):139-44.
6. Geyer SJ, Franzini DA. Myxomatous degeneration of the mitral valve complicated by nonbacterial thrombotic endocarditis with systemic embolization. Am J Clin Pathol 1979;72(3):481-92.
7. Saffro R, Talano JV. Transient attack associated with mitral systolic clicks. Arch Intern Med 1979;139:693-4.

8. Julien J, Lapuyade G, Lagueny A. Accident vascular cerebral chez des sujets avec un prolapsus de la valve mitrale: deux observations. Nour Press Med 1987;7:47.
9. Watson RT. TIA, stroke, and mitral valve prolapse. Neurology 1979;29(6):886-9.
10. Hanson MR, Conomy JP, Hodgman JR. Brain events associated with mitral valve prolapse. Stroke 1980;11(5):499-505.
11. Woldoff HS, Gerber M, Desser KF, et al. Retinal vascular lesions in two patients with prolapsed mitral valve leaflets. Am J Ophthalmol 1975;79(3):382-5.
12. Wilson LA, Keeling PW, Malcolm AD, et al. Visual complication of mitral leaflet prolapse. Br Med J 1977;2(6079):86-8.
13. Sandok BA, Giuliani ER. Cerebral ischemic events in patients with mitral valve prolapse. Stroke 1982;13(4):448-50.
14. Agarwal BL. Rheumatic heart disease unabated in developing countries. Lancet 1981;2(8252):910-1.
15. Al-Harthi SS, Husain IS, Al-Orainey IO, et al. Prevalence of mitral valve prolapse in presumably healthy young Saudi men. Ann Saudi Med 1988;8(1):40-2.
16. Barlow JB, Bosman CK. Aneurysmal protrusion of the posterior leaflet of the mitral valve: an auscultatory-electrocardiographic syndrome. Am Heart J 1966;71:166-78.
17. Warth DC, King ME, Cohen JM, et al. Prevalence of mitral valve prolapse in normal children. J Am Coll Cardiol 1985;5(5):1173-7.
18. Perloff JK, Child JS, Edwards JE. New guidelines for the clinical diagnosis of mitral valve prolapse. Am J Cardiol 1986;57:1124-9.
19. Abbasi AS, De Cristofaro D, Anabtawi J, Irwin L. Mitral valve prolapse: comparative value of M-mode, two-dimensional and Doppler echocardiography. J Am Coll Cardiol 1983;2(6):1219-23.
20. Boughner DR, Barnett HJ. The enigma of the risk of stroke in mitral valve prolapse. Stroke 1985;16(2):175-7.
21. Steele P, Weily H, Rainwater J, Vogel R. Platelet survival time and thromboembolism in patients with mitral valve prolapse. Circulation 1979;60(1):43-5.
22. Pomerance A. Ballooning deformity (mucoid degeneration) of atrioventricular valves. Br Heart J 1969;31:343-51.
23. Cook AW, Bird TD, Spencer AM, et al. Myotonic dystrophy, mitral-valve prolapse, and stroke. Lancet 1978;1(8059):355-6.
24. Bramlet DA, Decker EL, Floyd WL. Nonbacterial thrombotic endocarditis as a cause of stroke in mitral valve prolapse. South Med J 1982;75(9):1133-5.
25. Schnee MA, Bucal AA. Fatal embolism in mitral valve prolapse. Chest 1983;83(2):285-7.
26. Nishimura RA, McGoon MD, Shab C, et al. Echocardiographically documented mitral-valve prolapse: long-term follow-up of 237 patients. N Engl J Med 1985;313(21):1305-9.
27. Barletta GA, Gagliardi R, Benvenuti L, Fantini F. Cerebral ischemic attacks as a complication of aortic and mitral valve prolapse. Stroke 1985;16(2):219-23.

RECURRENT MENINGITIS ASSOCIATED WITH CONGENITAL DEAFNESS AND IgG SUBCLASS IMMUNODEFICIENCY: REPORT OF A CASE

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Recurrent meningitis in childhood is a well-recognized clinical entity often difficult to manage. Causes include a congenital or acquired gross anatomical defect permitting communication between skin, mucous membranes, or sinuses and the subarachnoid space, a persistent focus of infection elsewhere, or a disorder of the immune system.[1-4] This presentation illustrates the identification of the probable cause and treatment of recurrent pneumococcal meningitis in a 4-year-old boy.

Case Report

A 4-year-old Saudi boy was admitted to King Faisal Specialist Hospital and Research Centre on 17 December 1987 because of recurrent bacterial meningitis. Four attacks had occurred over the previous 18 months, and three were proved to be due to pneumococci by culture of the organism from the cerebrospinal fluid. The attack 7 days before admission was characterized by CSF polymorphonuclear pleocytosis, elevated CSF protein, and depressed CSF glucose, but smears and cultures of the CSF were negative for bacteria. As in the three previous occurrences, the patient was treated successfully with penicillin. A week after treatment began for the most recent infection, he was referred to KFSH & RC for further management. The attacks of meningitis had occurred on 18 September and 12 October 1986 and 29 October and 10 December 1987.

The patient was one of three siblings. Deafness was recognized at 9 months and resulted in the child's being mute. Adaptive behavior and motor landmarks were normal. The child had had no frequent infections or remarkable trauma in the past. The siblings, aged 6 and 1½ years, were in good health. The parents were first cousins, and no family members were deaf.

Clinical examination showed a well-nourished, well-developed male. Neurologic examination was normal, except for deaf-mutism. There was no rhinorrhea, otorrhea, or midline defect from the skull to the inferior sacrum.

Results of chemical analyses of blood and CSF as well as urinalysis were normal. Plain roentgenograms of the chest, skull, and sinuses appeared normal. Brainstem auditory evoked responses using a 75-dB click stimulus elicited normal electroencephalographic response. A plain CT scan of the brain oriented to the orbitomeatal line was normal. A CT scan of the petrous portion of the temporal bone showed opacification of the right mastoid cells. No abnormalities of the inner ear were seen.

A coronal CT scan with 1.5-mm sections through the anterior cranial fossa showed no abnormalities of the cribriform plate. A 99mTc DTPA cisternogram via a lumbar puncture showed normal flow of CSF and no evidence of paranasal sinus, middle ear, or mastoid leaks.

Following this an otolaryngologic consultation noted on tympanogram evidence of middle ear fluid on the right. In view of the history bilateral tympanotomy was performed and tubes were inserted. Fluid flowed 24 hours later from the right tube. It had the chemical characteristics of an effusion, and culture grew *Hemophilus influenzae*

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(untyped) and *Staphylococcus epidermidis*. Middle ear drainage ceased in 5 days.

Five days after the myringotomy and 7 days after the first cisternogram, a second 99mTc DTPA cisternogram was performed. Cotton pledgets were placed against the tympanotomy tubes and the tympanic membrane. The CSF flow pattern was normal, no evidence of extrasubarachnoidal flow was discerned, and gamma counts of the pledgets in a scintillation well counter showed no significant difference in the counts from background radiation. At the same time, a repeat CT scan of the temporal bone showed the mastoid antrum and air cells to be clear. The cochlea on both sides was of normal anatomy with no evidence of deformities or defects.

With no evidence of subarachnoid-sinus communication found, attention was directed to a study of the immune system. Serum total hemolytic complement (CH$_{50}$), C3, and C4, nitroblue tetrazolium test, leukocyte chemotaxis, and phagocytosis were studied, and all were normal. The major immunoglobulin classes in the serum were quantitated by a modified automated immunoprecipitation method.[5] Serum IgG subclasses were quantitated by radioimmunoassay method, and the results are shown in Tables 1 and 2.

TABLE 1. *Patient's serum immunoglobulin quantitated by a modified automated immunoprecipitation method.*

Patient level	Reference interval
IgG 6.36 g/L	3.44 – 11.80 g/L
IgA 1:84 g/L	0.02 – 0.55 g/L
IgM 1.08 g/L	0.19 – 1.04 g/L
IgE 91.2 ug/L	19.2 – 600 ug/L

TABLE 2. *Patient's serum IgG subclasses quantitated by radioimmunoassay.*

Patient level	Reference value
IgG1 4.52 g/L	5.8 ± 1.36 g/L
IgG2 < 0.10 g/L	1.74 ± 0.73 g/L
IgG3 0.5 g/L	0.48 ± 0.18 g/L
IgG4 < 0.01 g/L	0.25 ± 10 g/L

This patient therefore showed a deficiency in subclass IgG2 and IgG4. In addition, since the IgG concentration was in the middle of the normal range after a recent serious infection, which in a "normal" person would produce an elevated serum IgG, this patient might be considered to have lower than expected IgG.

The patient was treated in hospital with 5 days of intravenous penicillin and 7 days of oral penicillin. He was discharged home on prophylactic penicillin, 250 mg every 12 hours. The discharge diagnosis was recurrent pneumococcal meningitis, and there was no evidence of subarachnoid-sinus or mucous membrane communication, IgG2 and IgG4 subclass immunodeficiency, and congenital deaf-mutism.

Discussion

Recurrent bacterial meningitis is a serious problem and deserves a careful search to identify an underlying cause of the infection. Eighty percent of recurrent meningitis in midline defects is due to pneumococcal pneumonia. Although cranial anatomic and inner ear abnormalities are the commonest underlying causes of recurrent meningitis, the diagnosis can be extremely difficult. Special techniques using coronal thin-section cranial CT have been helpful in demonstrating a CSF-middle ear or basal communication.[6,7]

The major problem this patient presented was to identify a possible communication between the subarachnoid space and the skin, sinuses, or middle ear. Absence of a midline defect from scalp to coccyx narrowed the search. The presence of a congenital bilateral sensorineural hearing defect suggested the likelihood of an abnormality in the development of the labyrinthine capsule and stapes footplate, leading to a "labyrinthine gusher" syndrome.[8] Repeated CT scans of the temporal bone showed no abnormality of the inner ear. Also thin-section coronal anterior fossa CT scanning showed no defect in the cribriform plate, nor were minute defects leading to a subarachnoid-inner or middle ear communication defined by repeated isotope cisternography. The middle ear drainage through the right tympanotomy tube did not contain pneumococci, was not spinal fluid by chemical testing, and occurred after 17 days of penicillin treatment. Furthermore, the drainage stopped 3 days after penicillin was started. The mastoid clouding cleared, and the middle ear drainage appeared in the absence of an isotope-proved connection between the subarachnoid space and the middle ear. These occurrences were an epiphenomenon clearly not related to the pneumococcal meningitis.

In the absence of an anatomic abnormality, attention was directed to the patient's immune status. It was then shown that the patient had an IgG2 and IgG4 subclass deficiency. The possible relation between these deficiencies and the recurrent pneumococcal meningitis is worthy of conjecture.

When IgG subclass deficiencies occur, there is a tendency for a pattern of subclass linkage to exist. Thus, IgG2 and IgG4 deficiencies tend to occur together and are often associated with IgA and/or IgE major class deficiencies.[9] When subclass deficiencies occur, the patient may or may not have increased incidence of infection. In a study of children aged 12 to 32 months, those prone to otitis had significantly lower IgG2 concentrations than those with normal IgG2 concentrations. In patients with IgG2 and IgG4 deficiency, there was absence of antibody to polysaccharide antigen teichoic acid and the protein antigen of staphylococci.[10] Another study of children showed that those who were IgG2 deficient had serum antibody to capsular polysaccharide of *H. influenzae* b significantly lower than age-matched controls both before and after immunization with *H. influenzae* b polysaccharide antigen. The antibody to *H. influenzae* b is predominantly of IgG2 subclass. In these same patients who had normal IgG1 protein concentrations, antibody response to tetanus and diphtheria toxoids was normal, as anticipated, since antibody to these antigens is predominantly IgG1 subclass.[11] Finally, it appears that the IgG2 subclass is responsible specifically for antibody response to polysaccharide antigens, especially pneumococcal and *H. influenzae* b polysaccharides, and IgG subclass deficiency may lead to recurrent infections with these organisms. However, it is extremely unusual to have recurrent meningitis as the sole manifestation of IgG subclass deficiency. Instead, patients with this deficiency may have meningitis as a part of systemic pyogenic infection.

It is therefore possible that this patient's recurrent pneumococcal meningitis was abetted by the presence of IgG2 deficiency. On this basis, if daily oral antibiotic prophylaxis is not successful, immunization with multiple pneumococcal antigens (Pneumovax) can be considered. Such immunization has produced an increase in IgG2 type-specific subclass antibody when none was produced by type-specific pneumococcal bacteremia, pneumonia, and pleurisy.[12] Specific subclass antibody to pneumococcus was not available to us; therefore, it was not measured.

References

1. Clark JL, De Santo LW, Facer GW. Congenital deafness and spontaneous CSF otorrhea. Arch Otolaryngol 1978;104:163-6.
2. Bridger MW, Phelps PD. Recurrent meningitis due to congenital malformation of the inner ear. Br Med J 1983;286(6365):626-7.
3. Thong YH, Simpson DA, Muller-Eberhard HJ. Homozygous deficiency of the second component of complement presenting with recurrent bacterial meningitis. Arch Dis Child 1980;55(6):471-3.
4. Taylor CJ. Recurrent meningitis in a child with combined IgA deficiency and splenic hypoplasia (letter). Arch Dis Child 1981;56(6):486.
5. Richie RF. Automated immunoprecipitation analysis of serum proteins: structure, function, and genetic control. 2nd ed. New York: Academic Press, 1975:376-425.
6. Steele RW, MConnell JR, Jacobs RF, Mawk JR. Recurrent bacterial meningitis: coronal thin-section cranial computed tomography to delineate anatomic defects. Pediatrics 1985;76(6):950-3.
7. Harris HH. Cerebrospinal otorrhea and recurring meningitis: report of three cases. Laryngoscope 1978;88(10):1577-85.
8. Hipskind MM, Lindsay JR, Jones TD, et al. Recurrent meningitis and labyrinthine gusher, related to congenital defects of the labyrinthine capsule and stapes footplate. Laryngoscope 1976;86(5):682-9.
9. Heiner DC. Significance of immunoglobulin G subclasses. Am J Med 1984;76(3A):1-6.
10. Oxelius VA. Immunoglobulin G (IgG) subclasses and human disease. Am J Med 1984;76(3A):7-18.
11. Umetsu DT, Ambrosino DM, Quinti I, et al. Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG-subclass deficiency. N Engl J Med 1985;313(20):1247-51.
12. Matter L, Wilhelm JA, Angehrn W, et al. Selective antibody deficiency and recurrent pneumococcal bacteremia in a patient with Sjogren's syndrome, hyperimmunoglobulinemia G, and deficiencies of IgG2 and IgG4. N Engl J Med 1985;312(16):1039-42.

PULMONARY ASPERGILLOSIS DUE TO *ASPERGILLUS TERREUS* VAR. *AFRICANUS* IN ACUTE LEUKEMIA: REPORT OF A CASE AND REVIEW OF THE LITERATURE

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Pulmonary aspergillosis is a common opportunistic fungal infection in immunocompromised hosts.[1] The most frequently reported causative agents are *Aspergillus fumigatus* and *A. flavus*.[2] *Aspergillus terreus* has been shown to be a potential pathogen[3] and reported only rarely as an agent of human disease.[4-10] It is known to exist naturally in soils of warm parts of the world such as the southern United States[11]; it is also cultured from nails and postoperative mastoidectomy fenestration cavities.[12,13]

Herein, we report a case of multicavitary lung lesion caused by this organism with further identification as *A. terreus* var. *africanus* in a patient with relapsed acute lymphoblastic leukemia. To our knowledge, *A. terreus* var. *africanus* has never been reported to produce cavitary lung lesions in humans.

Case Report

A 30-year-old Saudi man was diagnosed to have acute lymphoblastic leukemia (ALL) in December 1984. He received induction chemotherapy at King Khalid University Hospital in Riyadh and achieved complete remission.

He was placed on maintenance chemotherapy until January 1986 when he was readmitted in his first relapse of ALL. At that time, he was ill-looking, pale, and febrile. He had a facial vesicular rash, left corneal ulcerations, bilateral fundal hemorrhage, oral thrush, and splenomegaly. His chest x-ray film appeared normal.

In addition to red blood cell and platelet transfusions, oral miconazole, and intravenous acyclovir, he received empiric carbenicillin and gentamicin. Hickman catheter insertion was done under vancomycin prophylaxis.

The patient responded well to initial treatment, and all antibiotics were discontinued by day 10 of reinduction chemotherapy. On day 12 he became febrile again. No focus of infection was detected, and his chest x-ray appeared normal. He received 3 days of carbenicillin and gentamicin, which were changed to cefotaxime after blood cultures grew a *Klebsiella oxytoca* resistant to carbenicillin. His fever subsided after 48 hours. On day 23, fever of 39°C occurred. He had a white blood cell count of 0.3×10^6/L. His chest x-ray film showed three ill-defined shadows, one in the right and two in the left middle zones. Empiric treatment with amphotericin B with a rapid dose build-up over 24 hours was started. Marked clinical improvement occurred. Serial chest x-ray films showed progression from ill-defined shadows to cannonball-like opacities (Figure 1), which enlarged and progressed into thin wall cavities, each of them containing a circular ball-like opaque mass freely movable within the cavity, characteristic of *Aspergillus* mycetoma (Figure 2). An additional thin wall cavity with a mycetoma ball in the right paraspinal region was seen on chest CT scanning (Figure 3). His leukocyte count rose to over 1×10^6/L at 10 days from the beginning of amphotericin B. Follow-up chest x-ray films showed resolution of the cavities and opacities with residual fibrotic changes in both middle zones (Figure 4).

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Immunodiffusion test performed on the patient's serum against *A. fumigatus* antigen was negative. The complete identification of the isolated *Aspergillus* organisms from the patient's sputum was reached and found to be *A. terreus* var. *africanus* (see below). Intravenous amphotericin B was given for a total dose of 1720 mg.

After his second complete remission, the patient was referred for bone marrow transplantation before which he suffered a second relapse. A third brief remission was achieved with combination chemotherapy, and only a partial remission of a third relapse was achieved with high-dose cytosine arabinoside. He expired in February

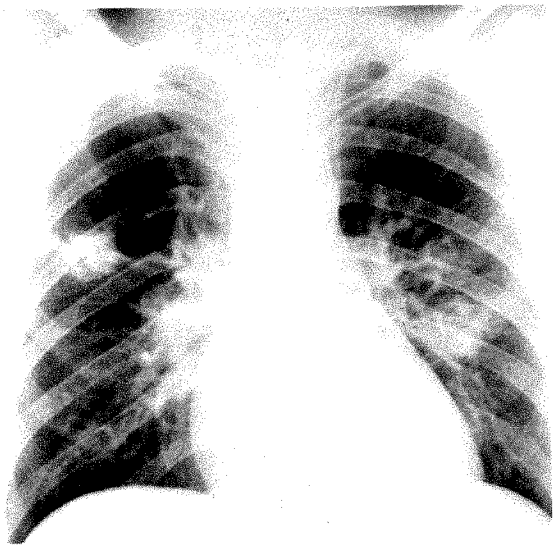

FIGURE 1. Chest x-ray film showing the three cannonball-like opacities, one on the right middle and two on the left middle zones.

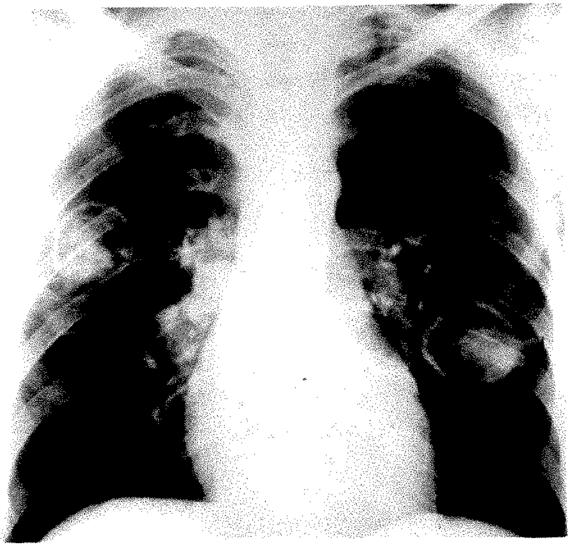

FIGURE 2. Chest x-ray film showing progression of the opacities into thin wall cavities which are seen with relatively small opaque balls.

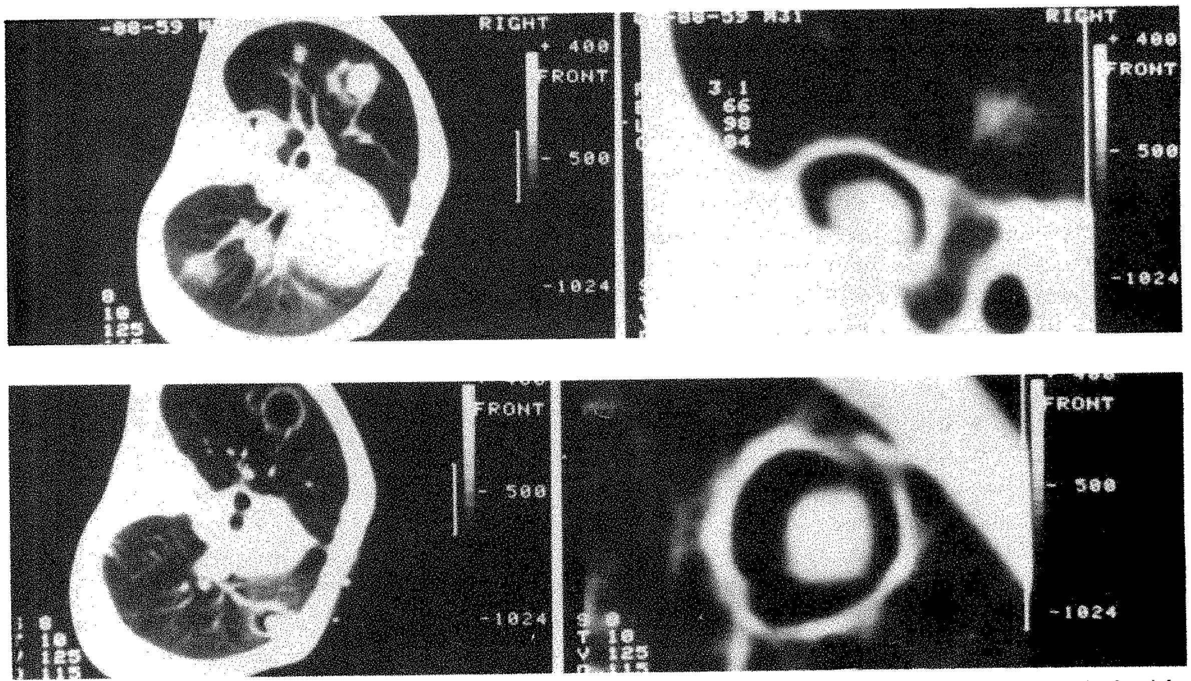

FIGURE 3. Chest CT scan showing the opaque balls to be freely movable and disclosing a fourth cavity and mycetoma in the right paravertebral region, not seen on plain chest radiography.

1987 of overwhelming acute leukemia. Throughout that 10-month period, he had no recurrence of his pulmonary aspergillosis.

Mycologic Findings

Examination of Giemsa-stained smears of sputum collected on 3 different days from the patient revealed presence of septate fungal hyphae in each specimen (Figure 5A). Culturing the patient's sputum on Sabouraud dextrose agar supplemented with chloramphenicol yielded the same fungus from each specimen. On Czapek solution agar, the fungal colonies (Figure 5B) were brown to cinnamon in color; the reverse was dark brown. When the organism was grown on oatmeal agar medium, it produced abundant, somewhat spherical, sclerotium-like structures (Figure 5C). Smooth conidiophores were produced by the fungus with columnar spore heads, biseriate sterigmata, and globose conidia (Figure 5D). Therefore, the organism was identified as *A. terreus* var. *africanus.*[14]

Discussion

We are aware of only nine cases of human systemic infections caused by *A. terreus*. Seligsohn, et al[4] compiled five cases of invasive aspergillosis caused by this organism. Their patient had osteomyelitis; the patient of Agarwal et al[8] had orbital aspergillosis; that of Mershon et al[9] had endocarditis and mycotic aneurysm; that of Mahgoub et al[10] had meningitis. Drexler et al[5] reported a case of infective endocarditis on a mitral valve porcine heterograft. In 1981, Laham et al reported a case of allergic bronchopulmonary aspergillosis caused by *A. terreus* in a 16-year-old patient with history of asthma and recurrent pneumonia.[6] And in 1982, two additional cases were reported by Laham and Carpenter[7]; one involved a 53-year-old patient with rheumatic heart disease and prosthetic aortic and mitral valves who had postmortem evidence of *A. terreus* endocarditis, and the other case was a "pulmonary mycetoma" that developed in a 58-year-old patient, with a history of tuberculosis, whose *A. terreus* was recovered from an expectorated fungus ball. Serum specimens from each of their three patients contained antibodies against *A. terreus* antigen.

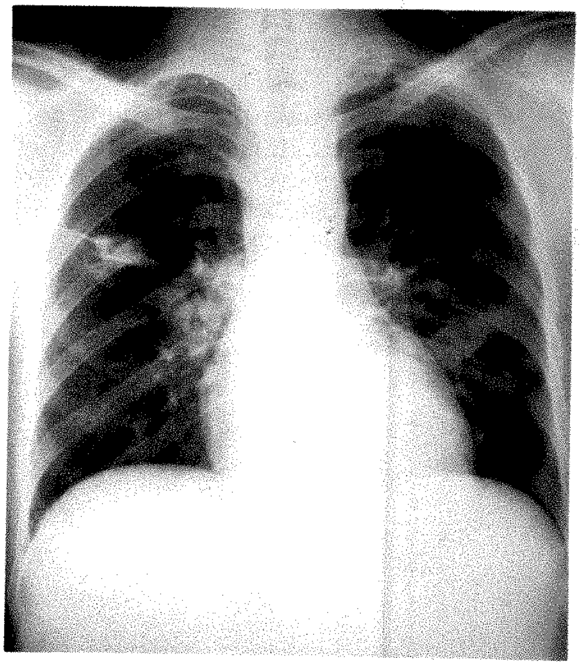

FIGURE 4. Follow-up chest x-ray film after amphotericin B therapy and neutrophil recovery, showing resolution of the mycetoma balls and the cavities with persistent residual fibrosis.

Our patient developed bilateral pulmonary infiltrates which progressed to multiple cavities that regressed to scarring and fibrosis. He was neutropenic and receiving broad-spectrum antibiotics for a gram-negative septicemia. The patient showed a remarkable clinical improvement accompanied by resolution of the pulmonary changes on the radiography over a period of 1 month. Our hypothesis of fungal pneumonia was confirmed by the isolation and identification of the fungus involved as *A. terreus* var. *africanus* from multiple sputum cultures. Isolation of *Aspergillus* organisms from respiratory secretions is considered sufficient for the diagnosis of aspergillosis in such a clinical and radiologic setting and especially in a highly predisposed leukemic patient with neutropenia and on broad-spectrum antibiotics. Invasive diagnostic procedures contribute relatively little to the management of these patients.[15,16] It may be important to note the occurrence of the *A. terreus* var. *africanus* as an opportunistic pathogen in Saudi Arabia, a country that has a warm climate; in the warm-climated southern and southwestern parts of the United States, *A. terreus* has been found and cultured much more frequently than in its northern cold-climate regions.[11] We are committed to concentrate further on these unusual pathogens as we see a relatively increased incidence of fungal pulmonary complications in our patients with acute leukemia.[17]

In summary, we describe a case of opportunistic pulmonary multicavitary aspergillosis due to *A. terreus* var. *africanus* in a patient with acute lymphoblastic leukemia. It occurred during his induction chemotherapy while leukopenic and on broad-spectrum antibiotics for gram-negative septicemia; it responded to amphotericin B and did not recur after repeated courses of chemotherapy and neutropenia.

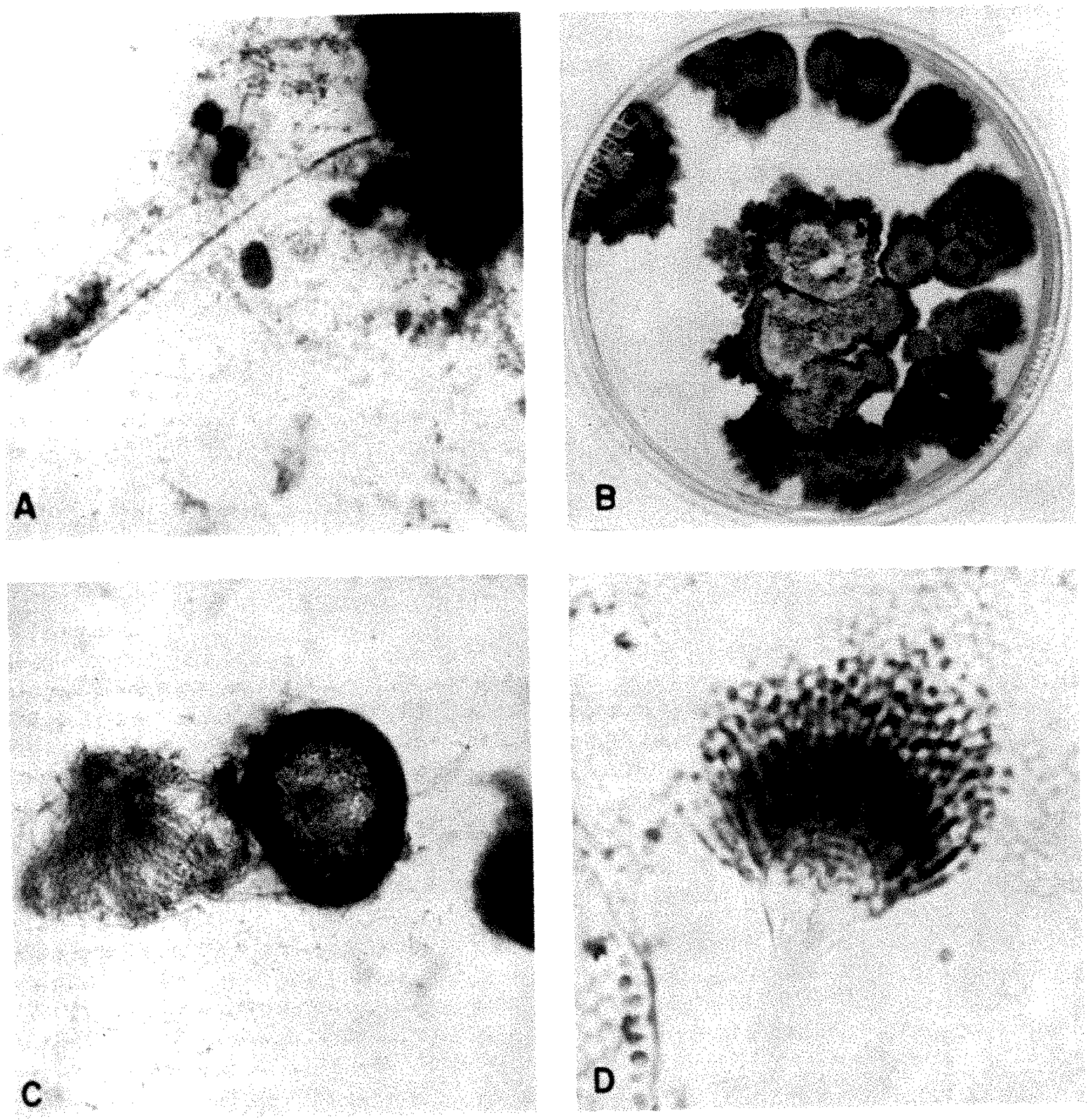

FIGURE 5. Photomicrographs of the patient's sputum smears and cultures. A, Hypha in a Giemsa-stained smear (original magnification, ×400). B, One-week-old fungal colonies on Czapek solution agar. C, Sclerotium-like structure seen after organism was grown on oatmeal agar medium (original magnification, ×250). D, Columnar spore head showing smooth conidiophore, biseriate sterigmata, and globose conidia (original magnification, ×1000). These features are diagnostic of *A. terreus* var. *africanus*.

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References

1. Meyer RD, Young LS, Armstrong D, et al. Aspergillosis complicating neoplastic disease. Am J Med 1973;54:6-15.
2. Rinaldi MG. Invasive aspergillosis. Rev Infect Dis 1983;5(6):1061-77.
3. Rippon JW, Anderson DN, Soo Hoo M. Aspergillus: comparative virulence, metabolic rate, growth rate and ubiquinone content of soil and human isolates of Aspergillus terreus. Sabouraudia 1971;12:157-61.
4. Seligsohn R, Rippon JW, Lerner SA. Aspergillus terreus osteomyelitis. Arch Intern Med 1977;137(7):918-20.
5. Drexler L, Rytel M, Keelan M, et al. Aspergillus terreus infective endocarditis on a porcine heterograft valve. J Thorac Cardiovasc Surg 1980;79(2):269-74.
6. Laham MN, Allen RC, Greene JC. Allergic bronchopulmonary aspergillosis (ABPA) caused by Aspergillus terreus: specific lymphocyte sensitization and antigen-directed serum opsonic activity. Ann Allergy 1981;46(2):74-80.
7. Laham MN, Carpenter JL. Aspergillus terreus, a pathogen capable of causing infection, endocarditis, pulmonary mycetoma, and allergic bronchopulmonary aspergillosis. Am Rev Resp Dis 1982;125(6):769-72.
8. Agarwal LP, Malik SRK, Mohan M, et al. Case notes: orbital aspergillosis. Br J Ophthalmol 1962;46:559-62.
9. Mershon JC, Samuelson DR, Layman TE. Left ventricular "fibrous body" aneurysm caused by Aspergillus endocarditis. Am J Cardiol 1968;22:281-5.
10. Mahgoub ES, Ismail SA, El-Hassan AM. Cervical lymphadenopathy caused by Aspergillus terreus. Br Med J 1969;1:689-90.
11. Laham MN, Jeffrey B, Carpenter JL. Frequency of clinical isolation and winter prevalence of different Aspergillus species at a large southwestern army medical center. Ann Allergy 1982;48(4):215-9.
12. Zaias N. Onychomycosis. Arch Dermatol 1972;105:263-74.
13. English MP. An outbreak of fungal infections of post-operative oral cavities. J Laryngol 1962;76:1-11.
14. Paper KB, Fennell DI. The genus Aspergillus. Baltimore: Williams and Wilkins, 1965:82-11,567-77.
15. Nalesnik MA, Myerowitz RL, Jenkins R, et al. Significance of Aspergillus species isolated from respiratory secretions in the diagnosis of invasive pulmonary aspergillosis. J Clin Microbiol 1980;11(4):370-6.
16. Robertson MJ, Larson RA. Recurrent fungal pneumonias in patients with acute nonlymphocytic leukemia undergoing multiple courses of intensive chemotherapy. Am J Med 1988;84:233-9.
17. El Saghir NS, Ajarim DS, Hall AD, et al. Adult acute nonlymphocytic leukemia in Saudi Arabia: experience at King Khalid University Hospital in Riyadh. Ann Saudi Med 1989;9(2):158-64.

FACTITIOUS DEEP VENOUS OCCLUSION: REPORT OF A CASE

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Whenever patients defy an accurate diagnosis, factitious illness should be kept in mind.[1,2] Factitious disorders have been confused with Munchausen's syndrome, which is generally seen in male vagrants, who present to different emergency rooms with complex, dramatic, and untruthful stories. Patients with factitious disorders are most often young, intelligent, single women with an immature personality and a childhood history of neglect or abuse. They usually present with a single, plausible complaint and subject themselves willingly to unnecessary investigations and therapies. Only with time does fabrication become evident.[1] To our knowledge, this is the first reported case of self-induced, recurrent, unilateral peripheral venous occlusion.

Case Report

A 45-year-old woman on warfarin was admitted with deep venous thrombosis (DVT) of her left arm. She had presented at another clinic 6 weeks previously with a 10-day history of progressive left leg swelling. She was diagnosed without venography as having DVT, and anticoagulation therapy was prescribed. During that hospitalization, she developed a swollen left arm, which initially improved on warfarin. She had a 10-year history of probable rheumatoid arthritis complicated by sicca syndrome and symptomatic pericarditis.

Medical history included a total knee replacement, an L4-5 laminectomy for disk prolapse, drug-induced gastric ulcerations, cholecystectomy, appendectomy, and removal of breast abscess. Hysterical seizures were diagnosed a year previously, after an EEG during an attack showed no epileptiform discharges.

Examination revealed a swollen left arm with a few petechiae, ecchymoses, and a rather abrupt demarcation to the normal proximal upper arm. Her right leg was normal. Contrast venography of the right leg veins was normal; left arm venogram is shown in Figure 1. A CT scan of the left arm was normal. Prothrombin time (PT) was in the therapeutic range. Hematocrit, platelet count, thrombin time, serum fibrinogen, and antithrombin III levels were normal, and lupus anticoagulant was absent. She was discharged on warfarin but stopped it after 14 days because of menorrhagia.

Two weeks later she was readmitted with painful swelling of her right leg from the mid thigh of 8 days' duration. PT and partial thromboplastin time were normal as was venography. Right leg ultrasonography excluded a Baker's cyst. Right thigh and pelvic lymphangiography and CT were normal. On the seventh hospital day, she was seen fidgeting under the blanket. An elastic bandage was found wrapped seven times very tightly around her mid thigh. She admitted to having induced the swelling in both legs but not in her arm. She was referred to a psychiatrist. She cooperated poorly with the psychiatrist, but undoubtedly had serious family problems which she refused to detail. She had an inappropriate, indifferent attitude to her illness, and appeared lonely and mildly depressed.

Discussion

The following features should have suggested the diagnosis during the patient's first admission—her previously documented hypochondriacal personality and hysterical seizures, the development of venous occlusion while on

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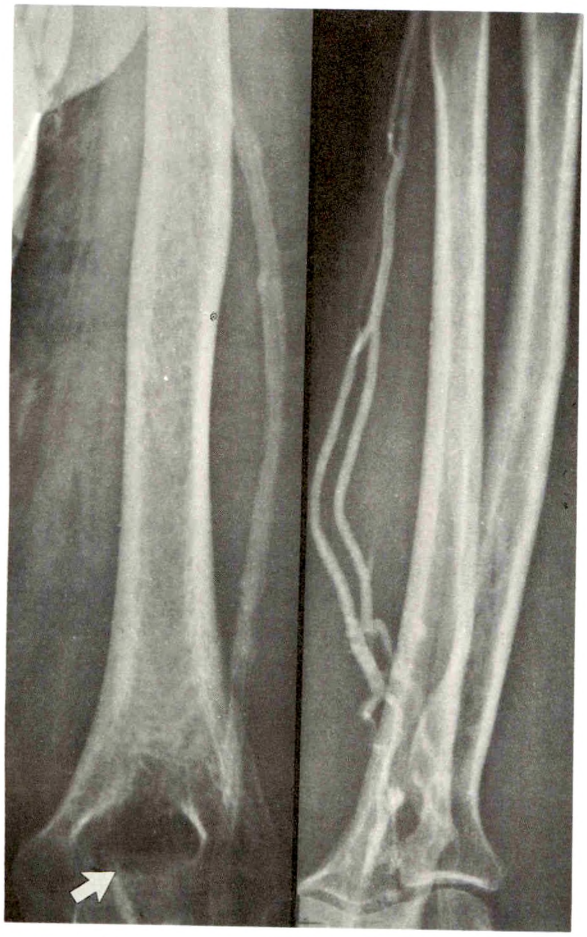

FIGURE 1. Contrast venogram of the left arm without use of tourniquet. There was no filling of the deep veins of the forearm or upper arm and incomplete filling of the superficial veins of the forearm. Normal filling of the cephalic vein occurred, but the basilic vein was obstructed just above the elbow joint (arrow). No thrombus was seen.

adequate anticoagulation, and the intractable worsening of her arm edema as an outpatient which quickly subsided in hospital. Even without this background, the following signs should alert the physician to factitious peripheral edema and venous occlusion: (1) the upper limb venous occlusion occurred on the left side in a right handed patient; (2) there was a rather abrupt demarcation between the edema and the normal proximal part of the limb secondary to the tourniquet; (3) the edematous skin showed on one occasion some petechiae and small ecchymoses suggesting complete venous obstruction for some time; and (4) the venograms either were normal or showed occlusion of the deep veins, probably due to external compression by the surrounding marked soft tissue edema (Figure 1), and thrombus was never demonstrated.

Considering the potential dangers of anticoagulation[3] and the expense of extensive investigations, early recognition of this is clearly important. In suspected cases, hospital admission, preferably in a room with television surveillance and frequent random nursing checks, is recommended. One wonders how many of her four previous operations have been for genuine disease entities.

References

1. Scoggin CH. Factitious illness: dramatic deceit versus reality. Postgrad Med 1983;74(5):259-65.
2. Folks DG, Freeman AM 3rd. Munchausen's syndrome and other factitious illness. Psychiatr Clin North Am 1985;8(2):263-78.
3. Levine MN, Raskob G, Hirsh J. Hemorrhagic complications of long-term anticoagulation therapy. Chest 1986;2(suppl):16S-25S.

CLEAR CELL ADENOCARCINOMA OF THE VAGINA: CASE REPORT AND REVIEW OF THE LITERATURE

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Carcinomas of the vagina are uncommon[1,2] and are usually squamous cell in type. Over the past few decades, however, the incidence of vaginal adenocarcinomas has increased, predominantly of the clear cell type and mainly affecting younger subjects.[1,3-5]

In 1970 Herbst and Scully[6] described clear cell adenocarcinoma of the vagina in six girls and young adults and subsequently confirmed its association with exposure to diethylstilbestrol (DES) in utero. Since then, numerous reports of the condition have appeared in the medical literature.[5] By 1980 over 400 cases have been reported from various parts of the world,[5,7,8] the majority being in the United States.

The first case in the United Kingdom was that reported by Monaghan and Sirisena in 1978.[9] By 1984 only four cases had been reported in the UK.[8] The variation in incidence of the disease in different parts of the world is a reflection of the extent to which mothers were treated with DES during pregnancy for threatened or habitual abortion in the different countries.

We present the first report of clear cell adenocarcinoma of the vagina in a 23-year-old Arab woman. Exposure to DES in utero could not be confirmed in this case, but the presence of the condition raises many issues which are discussed in this paper.

Case Report

A 23-year-old Yemeni woman had a 2-month history of swelling of left lower limb, associated with vague suprapubic pain, dysuria, and hematuria. She also had bilateral inguinal swelling. She gave no history of relevant previous illness or drug ingestion. She was para 3, all dead (one neonatal death and two stillbirths).

Examination revealed a hard supraclavicular lymph node on the right side with smaller ones in the posterior triangle. The abdomen showed suprapubic tenderness and an enlarged, smooth, nontender liver. Enlarged inguinal nodes were noted on both sides, and the entire left lower limb was swollen and tender. Rectal examination revealed hard masses filling the vagina anteriorly and to the left, confirmed by vaginal examination. Gynecologic examination under anesthesia revealed normal vulva and a firm, irregular, friable mass, filling the upper vagina and destroying the cervix, with associated malodorous, blood-tinged discharge. The uterus was bulky and immobile. The fornices were thickened, suggesting parametrial involvement. Biopsy specimens were taken from the vaginal mass and the supraclavicular lymph node. Cystoscopic examination showed slightly congested bladder mucosa with no obvious tumor infiltration of the wall.

Other investigations revealed microcytic, hypochromic anemia with hemoglobin of 82 g/L and erythrocyte sedimentation rate of 80 mm/h. Results of biochemical investigations were within normal limits. Chest x-ray appearance was normal, but abdominal roentgenogram showed spina bifida at S1 and right-sided psoas mass containing streaks of calcification. Renal shadows were normal, and x-ray examination of the left leg showed only soft tissue swelling. Results of microbiologi-

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cal investigations were noncontributory.

Histopathologic examination of a vaginal lesion showed malignant neoplasm composed of clear cells forming sheets as well as tubular structures (Figure 1). Papillary areas were also present (Figure 2). The cells showed moderate pleomorphism. Special stains showed high glycogen content of the cells as well as lipid. Immunohistochemical analyses for alpha-fetoprotein and carcinoembryonic protein were both negative. The supraclavicular lymph node demonstrated extensive replacement by metastatic clear cell carcinoma with features similar to the vaginal lesion. A histologic diagnosis was made of clear cell adenocarcinoma of the vagina metastatic to supraclavicular lymph nodes. The patient was referred for chemotherapy on account of the advanced nature of the disease.

No relationship to DES exposure could be ascertained from direct questioning of the patient and her relatives. Extensive investigation of the kidneys ruled out renal cell carcinoma metastatic to the vagina and cervix. Primary carcinoma of the ovaries was also excluded.

Discussion

Carcinoma of the vagina is rare in Saudi Arabia, as evidenced by its absence from reports of various epidemiologic and hospital-based studies of cancer in the Kingdom.[10-14] To our knowledge, this is the first case of clear cell adenocarcinoma of the vagina to be reported in the Eastern Province of Saudi Arabia. Since the initial documentation of association between DES exposure and clear cell adenocarcinoma of the female genital tract by Herbst et al in 1971,[15] subsequent studies on the pathogenesis[16-22] and other morphologic changes in the female genital system[23-27] have been reported extensively. Changes in the DES-exposed male, especially the genital system, have also been described.[8,16,28] Owing to the late presentation of our case with evidence of local and distant spread, it was not possible to assess the presence of any of the other lesions reportedly associated with DES exposure.

Further evidence of association between DES exposure and clear cell adenocarcinoma of the vagina is the finding[15] that most of the affected girls were born between 1946 and 1951, the period when the use of DES and related compounds was at its peak. Two thirds of the cases reviewed by Herbst et al in 1979[16] had a history of exposure during the first trimester of pregnancy. This association could not be proved in our cases, but the young age of the patient could be regarded as highly suggestive. With cessation of use of that drug in pregnancy, a reduction in incidence of the disease has been described,[5,8] and numbers reported from the United States are said to have reached a plateau.[8]

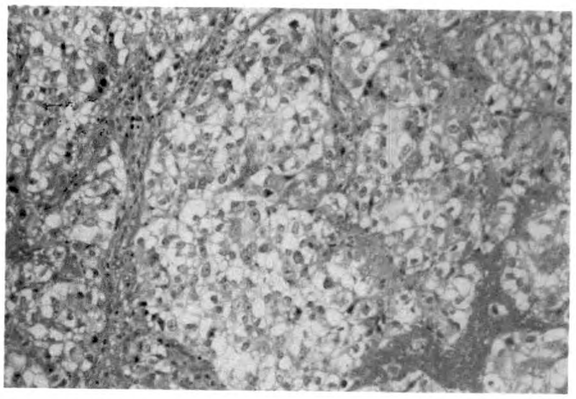

FIGURE 1. Adenocarcinoma showing clear cells with only slight nuclear pleomorphism (hematoxylin and eosin stain, original magnification, ×240).

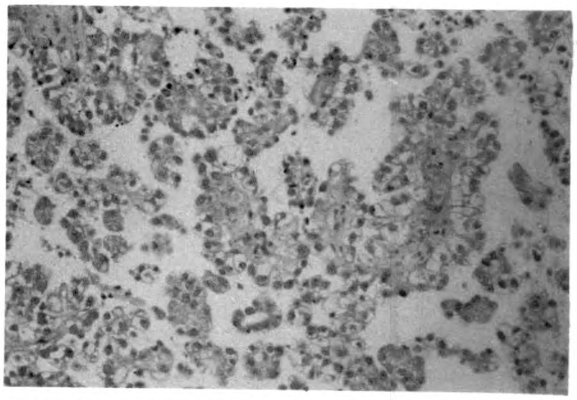

FIGURE 2. Clear cell adenocarcinoma of the vagina showing papillary structures (hematoxylin and eosin stain, original magnification, ×240).

Our case would indicate that clear cell adenocarcinoma in young women exists in Saudi Arabia. Increased awareness of this disease is necessary, in order to determine its association with DES exposure, if any, in this region. For this reason, we consider this report necessary. The patient presented very late (stage IV), and the prognosis at this stage is generally poor.[16] The increased awareness of the condition in the United States and Europe, generated by the first report of Herbst et al[6] and subsequent establishment of a register for new cases, has helped to ensure early detection of the tumor in subjects at risk. Follow-up studies of women at risk have indicated progression from benign lesions to clear cell adenocarcinoma of the vagina.[18,23,29-31] As history of DES exposure may not be available in many cases, especially in developing countries, it is essential for clinicians to recognize lesions reported to be associated with DES exposure so that women at risk can benefit from regular gynecologic follow-up and early detection of carcinoma and treatment. In centers where this has been done, 5-year survival has been reported to be as good as 80% to 90%. Staging of the disease and follow-up studies have been reviewed extensively in the literature.[16]

The effect of DES exposure on the mother herself has been investigated extensively. As yet, no definite picture has emerged, although some workers have reported an increase in premalignant conditions of the genital tract,[22] increased risk of breast cancer,[32] and ovarian cancer[33] in these women. A more careful study of women presenting with gynecologic malignancies in relation to DES exposure may help assess the extent of the problem in both mothers and offspring at risk in this region.

References

1. Johnston GA Jr, Klotz J, Boutselis JG. Primary invasive carcinoma of the vagina. Surg Gynecol Obstet 1983;156(1):34-40.
2. Rutledge F. Cancer of the vagina. Am J Obstet Gynecol 1967;97:633-55.
3. Herbst AL. Clear cell adenocarcinoma and the current status of DES-exposed females. Cancer 1981;48(2):484-8.
4. Veridiano NP, Tancer ML, Delke I, et al. Delayed onset of clear cell adenocarcinoma of the vagina in DES-exposed progeny. Obstet Gynecol 1981;57(3):395-8.
5. Herbst AL. The current status of the DES-exposed population. Obstet Gynecol Annu 1981;10:267-78.
6. Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence: a report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). Cancer 1970;25:745-75.
7. Herbst AL, Anderson D. Clinical correlations and management of clear cell adenocarcinoma. In: Herbst AL, Bern HA, eds. Developmental effects of diethylstilbestrol (DES) in pregnancy. New York: Thieme-Stratten, 1981.
8. Emens M. Vaginal adenosis and diethylstilboestrol. Br J Hosp Med 1984;31(1):42-8.
9. Monaghan JM, Sirisena LA. Stilboestrol and vaginal clear-cell adenocarcinoma syndrome. Br Med J 1978;1(6127):1588-90.
10. El-Akkad S. Cancer in Saudi Arabia: a comparative study. Saudi Med J 1983;4:156-64.
11. El-Akkad SM, Amer MH, Lin GS, et al. Pattern of cancer in Saudi Arabs referred to King Faisal Specialist Hospital in Saudi Arabia. Cancer 1986;58(5):1172-8.
12. Perrine RP, Jumaa A, cited by El-Akkad S. Cancer in Saudi Arabia: a comparative study. Saudi Med J 1983;4:156-64.
13. Mahboubi E. Epidemiology of cancer in Saudi Arabia, 1975-1985. Ann Saudi Med 1987;7(4):265-76.
14. Stirling GA, Khalil AM, Nada GH, et al. Study of one thousand consecutive malignant neoplasms in Saudis 1975-1977. Saudi Med J 1979;1(2):89-94.
15. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971;284:878-81.
16. Herbst AL, Norusis MJ, Rosenow PJ, et al. An analysis of 346 cases of clear cell adenocarcinoma of the vagina and cervix with emphasis on recurrence and survival. Gynecol Oncol 1979;7(2):111-22.
17. Silverberg SG, DeGiorgi LS. Clear cell carcinoma of the vagina: a clinical, pathological and electron microscopic study. Cancer 1972;29:1680-90.
18. Mattingly RF, Stafl A. Cancer risk in diethylstilbestrol-exposed offspring. Am J Obstet Gynecol 1976;126(5):543-8.
19. Robboy SJ, Taguchi O, Cunha GR. Normal development of the human female reproductive tract and alterations resulting from experimental exposure to diethylstilbestrol. Hum Pathol 1982;13(3):190-8.
20. Robboy SJ. A hypothetic mechanism of diethylstilbestrol (DES)-induced anomalies in exposed progeny. Hum Pathol 1983;14(10):831-3.
21. Sandberg EC. Benign cervical and vaginal changes associated with exposure to stilbestrol in utero. Am J Obstet 1976;125(6):777-89.
22. Bibbo M, Haenszel WM, Wied GL, et al. A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. N Engl J Med 1978;298(14):763-7.
23. Herbst AL, Kurman RJ, Scully RE. Vaginal and cervical adenosis after exposure to stilbestrol in utero. Obstet Gynecol 1972;40:287-98.
24. Robboy SJ, Kaufman RH, Prat J, et al. Pathologic findings in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) project. Obst Gynecol 1979;53(3):309-17.
25. Robboy SJ, Young RH, Welch WR, et al. Atypical vaginal adenosis and cervical ectropion: association with clear cell adenocarcinoma in diethylstilbestrol-exposed offspring. Cancer 1984;54:869-75.
26. Ulfelder H. Stilbestrol, adenosis and adenocarcinoma. Am J Obstet Gynecol 1973;117(6):794-800.
27. Sandberg EC, Danielson RW, Cauwet RW, et al. Adenosis vaginae. Am J Obstet Gynecol 1965;93:209-22.
28. Bibbo M, Gill WB, Azizi F, et al. Follow-up study of male and female offspring of DES-exposed mothers. Obstet Gynecol 1977;49(1):1-8.
29. Kaufman RH, Korhonen MO, Strama T, et al. Development of clear cell adenocarcinoma in DES-exposed offspring under observation. Obstet Gynecol 1982;59(6

suppl):68S-72S.
30. Ghosh TK, Cera PJ. Transition of benign vaginal adenosis to clear cell adenocarcinoma. Obstet Gynecol 1983;61(1):126-30.
31. Robboy SJ, Welch WR, Young RH, et al. Topographic relation of cervical ectropion and vaginal adenosis to clear cell adenocarcinoma. Obstet Gynecol 1982;60(5):546-51.
32. Greenberg ER, Barnes AB, Resseguie L, et al. Breast cancer in mothers given diethylstilbestrol in pregnancy. N Engl J Med 1984;311(22):1393-8.
33. Cohen I, Altaras M, Jaffe R, et al. Ovarian cancer in women given diethylstilbestrol in pregnancy: two case reports. J Pathol 1987;152(2):95-7.

VIRILIZING ADRENOCORTICAL CARCINOMA IN A 4-YEAR-OLD GIRL WITH FATAL RECURRENCE

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Adrenocortical tumors are rare in children.[1] The great majority are hormone secreting, and they produce androgens, glucocorticoids, a mixture of both, or rarely, estrogen or aldosterone.[2]

In this report, we describe a young girl who had virilization due to adrenocortical carcinoma that recurred after surgical removal.

Case Report

A 4-year-old girl was referred with a 6-month history of increasing pubic and facial hair and clitoral enlargement. She was the product of an uncomplicated pregnancy, labor, and delivery. The mother did not take any hormonal therapy during pregnancy. The patient had a healthy 10-year-old brother; her parents were not related. There was no family history of abnormal sexual development or deaths in early infancy suggestive of adrenal crisis.

At presentation, her weight was 112 cm and weight was 20 kg, both more than 2SD for her age. Blood pressure was 98/65 mm Hg. There was fine hair over the upper lip and dark coarse pubic hair. The clitoris measured 2.5 × 1 cm. Vaginal and urethral orifices were separate, with no labial fusion. There was no breast development, axillary hair, or abdominal masses. No signs of Cushing's syndrome were noted. There were no congenital anomalies.

Investigations showed normal results for complete hemogram, serum electrolytes, urea, creatinine, morning and evening cortisol and adrenocorticotropic hormone (ACTH), 17-hydroxyprogestrone, 11-desoxycorticosterone, 17-hydroxypregnenolone, aldosterone, and urinary 17-hydroxycorticosteroids. The karyotype was 46,××.

Abnormal laboratory results included serum testosterone of 12.3 nmol/L (reference interval, 0.7 to 3.5 nmol/L); dehydroepiandrosterone sulfate (DHAS), 25.7 μmol/L (reference interval, 0.3 to 1.6 μmol/L); and total urinary 17-ketosteroids, 110 μmol/d (reference value, < 6.93 μmol/d). The radiologic studies showed a bone age of 9 years; the plain film of the abdomen showed calcification in the region of the left suprarenal gland; the skull and chest x-ray appearances were normal. Ultrasonography of the adrenals showed a left suprarenal mass about 5 × 6 cm. It had a hyperechoic center suggestive of calcification (Figure 1), and the ovaries were normal. The intravenous urogram demonstrated a left suprarenal mass with calcification, displacing the left kidney downward. Computerized tomography (CT) of the abdomen showed a left suprarenal mass with normal liver and spleen (Figure 2).

Left adrenalectomy was performed, and a tumor 7 cm in diameter was removed. Local extension of the tumor to the diaphragm and perirenal fat were noted. On microscopic examination, the tumor cells demonstrated considerable pleomorphism, relatively high mitotic index (5 to 20 mitoses per 10 high-power fields), with areas of hemorrhage and necrosis. The pathologic diagnosis was adrenocortical carcinoma. Postoperative DHAS and testosterone levels initially fell to normal (Table 1), and pubic and facial hair ceased to grow. She was observed in the outpatient clinic at regular intervals to assess her clinical, hormonal, and radiologic condition.

Five months after operation, pubic and facial

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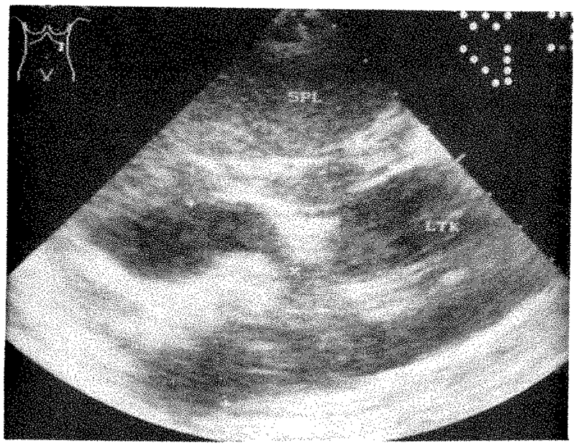

FIGURE 1. Ultrasonogram of the left adrenal tumor (marked), spleen (SPL), and left kidney (LTK).

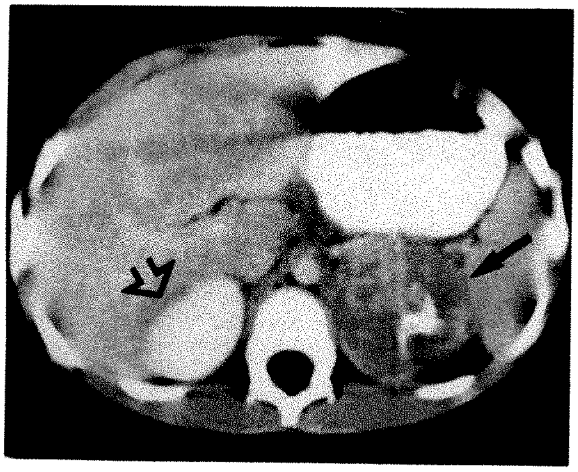

FIGURE 2. CT scan of the region of adrenal tumor showing the right kidney (white arrow) and the left suprarenal tumor with calcification (black arrow).

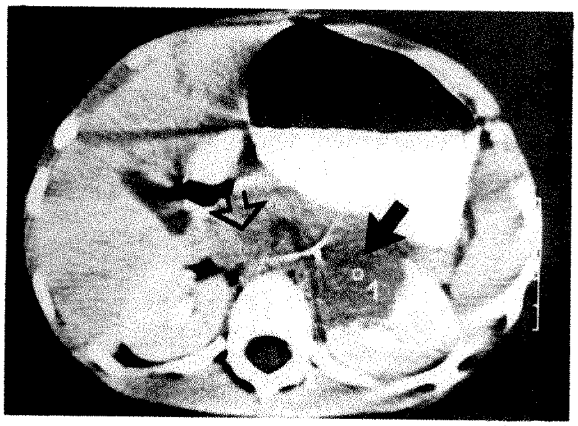

FIGURE 3. CT showing recurrence of the left adrenal carcinoma infiltrating the left kidney (black arrow) with enlargement of the para-aortic lymph nodes (white arrow).

TABLE 1. *Plasma values.*

Hormone (reference interval)	Preoperative	Postoperative 1 mo	Postoperative 5 mo.
Testosterone (0.35 – 0.7 nmol/L)	12.3	0.1	9.7
DHAS (0.3 – 1.6 μmol/L)	25.7	0.13	23.6
Urinary 17-ketosteroids (< 6.9 μmol/L)	110	1.9	81.3

hair started to reappear. The CT scan showed recurrence of malignant mass lesion displacing and infiltrating the left kidney with large para-aortic lymph nodes in the lumbar region (Figure 3) with metastases in both lungs. Testosterone and DHAS levels were markedly elevated (Table 1). The patient was then given mitotane without a positive response, and she died 4 months later.

Discussion

Adrenocortical tumors causing virilization are extremely rare in children.[3] These tumors secrete large quantities of dehydroepiandrosterone, a weak androgen with peripheral conversion into the more potent androgens, androstenedione and testosterone, both of which are responsible for virilization.[4] However, testosterone-secreting tumors occur rarely.[5] In prepubertal girls, excess androgen production is associated with rapid growth, facial and pubic hair, and clitoral enlargement,[2] as in our case. Posterior labial fusion had not been associated with adrenal tumors diagnosed after the neonatal period, due to the late exposure to excess androgens, in contrast with congenital adrenal hyperplasia, the most frequent cause of virilization in girls, in whom excessive production of androgens in utero is responsible for this abnormality. In addition, the finding of normal plasma levels of 17-OH-progesterone, 11-deoxycortisol, and 17-hydroxypregnenolone, depending on the nature of the deficiency, will rule out congenital adrenal hyperplasia. In ovarian tumors, another cause of female virilization, the tumor is often palpable by rectoabdominal examination. The finding of a high level of plasma testosterone in the presence of only slightly or moderately increased levels of 17-ketosteroids may point to an ovarian source of androgens.[6]

Prompt localization of adrenal tumors is important because of the possibility of malignant spread and rapid acceleration of skeletal maturation which may compromise adult stature. Recently, abdominal ultrasonography and CT scan have proved reliable in detecting adrenal tumors as small as 1 cm in diameter.[7-9] They replace the less accurate intravenous urography and the more invasive adrenal arteriography. Their value was evident in our patient, in diagnosing both the original tumor and the recurrent malignancy with metastases.

Histologic differentiation between adrenocortical carcinoma and adenoma is very difficult,[6] and sometimes only metastases confirm the diagnosis of malignant tumor. There is no close correlation between the pathologic appearance and the clinical course of the disease, as tumors with histologic features typical of malignancy may not metastasize for years, whereas tumors with a benign appearance may metastasize rapidly.[10]

Surgery is the definitive form of therapy to prevent adverse effects on growth and to avoid metastasis. The value of radiotherapy and chemotherapy in cases of malignant adrenal tumors in children is still debatable.[11]

Early reports described adrenocortical tumors in children as a serious disease with only 18% survival for more than 2 years, yet more recent series have shown a much better prognosis.[3,12] Many of the deaths reported in the earlier literature may have been due to postoperative complications and inadequate steroid replacement in the perioperative period. However, local recurrence after surgical excision of the tumor with distant metastases, as in our patient, is usually associated with fatal outcome within 7 months, even with use of mitotane.[13]

Patients with adrenocortical carcinoma should be monitored regularly by clinical examination, adrenal steroid assays, and ultrasound and CT for early detection of recurrence or metastases for prompt intervention.

References

1. Stewart DR, Jones PH, Jolleys A. Carcinoma of the adrenal gland in children. J Pediatr Surg 1974;9:59-67.
2. Hayles AB, Hahn HB Jr, Sprague RG, et al. Hormone-secreting tumors of the adrenal cortex in children. Pediatrics 1966;37:19-25.
3. Lee PD, Winter RJ, Green OC. Virilizing adrenocortical tumors in childhood: eight cases and a review of the literature. Pediatrics 1985;76(3):437-44.
4. Clayten GW, Holcombe JH. Adrenal tumors causing virilization. In: Suton WW, Viettl JD, Fernbach JD, eds. Clinical pediatric oncology. St. Louis: CV Mosby, 1977:687-9.
5. Kamilaris TC, DeBold CR, Manolas JK, et al. Testosterone-secreting adrenal adenoma in a peripubertal girl. JAMA 1987;258(18):2558-61.
6. Pardo JM. Virilization of a female infant due to an adrenal tumor. Clin Pediatr 1986;25(9):456-8.
7. Kaplowitz PB, Mandell J. Virilizing adrenal tumor in a 3-year-old girl: diagnosis by computed tomographic scan and ultrasound. Am J Dis Child 1983;137(4):406-7.
8. Davies RP, Lam AH. Adrenocortical neoplasm in children: ultrasound appearance. J Ultrasound Med 1987;6(6):325-8.
9. Falke TH, van Steters AP, Schaberg A, Moolenaar AJ. Computed tomography in untreated adults with virilizing congenital adrenal cortical hyperplasia. Clin Radiol 1986;37(2):155-60.
10. Baulieu EE, Peillan F, Migean CJ. Adrenogenital syndrome. In: Eisenstein AB, ed. The adrenal cortex. Boston: Little, Brown, 1967:533-637.
11. Cacciari E, Cicognani A, Pirazzoli P, et al. Adrenocortical tumours in children: our experience with nine cases. Acta Endocrinol 1986;279:264-74.
12. Zaitoon MM, Mackie GG. Adrenal cortical tumors in children. Urology 1978;12:645-50.
13. Didolkar MS, Bescher RA, Elias EG, Moore RH. Natural history of adrenal cortical carcinoma: a clinicopathologic study of 42 patients. Cancer 1981;47(9):2153-61.

Letters to the Editor

The *Annals of Saudi Medicine* welcomes letters to the Editor from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-spaced, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication, letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within 6 weeks of the article's publication.

Regional Variation in Sickle Cell Anemia in Saudi Arabia

To the Editor: The paper by Roberts et al[1] examined the effect of fetal hemoglobin (HbF) level and mean corpuscular volume (MCV) in sickle cell anemia patients from different regions of Saudi Arabia and related the findings to clinical and hematologic features in these patients. I find several ambiguities and deficiencies in the paper and would like to point out the major ones.

In the Materials and Methods section, Roberts et al stated that any patient with sickle cell anemia and an MCV level less than 80 fL was excluded from this study unless the parents' genotype was AS. By doing so, they claimed that Sβ-thalassemia patients were excluded. In the Results section, a large number of patients have MCV less than 80 fL, which may be due to either associated α-thalassemia or iron deficiency, since the authors ruled out Sβ-thalassemia on the basis of family studies and HbA_2 level. Roberts et al should have identified the cause of low MCV before correlating the severity of MCV. Furthermore, the comparison of clinical severity should be made between patients with similar MCV in different regions to see whether the severity index is the same or not.

In the paper, iron deficiency was not suspected in these patients despite the fact that no iron estimation or ferritin estimation was carried out. This was based on the assumption that one study from western Arabia in 1984 reported a normal serum ferritin level in 37 sickle cell anemia patients.[2] Is it scientifically correct to assume that if there was no iron deficiency report in one study on sickle cell anemia patients, then none of the patients will ever have iron deficiency? We have encountered a number of sickle cell anemia patients with iron deficiency during our investigations.

The other point related to α-thalassemia, which also results in low MCV, and mild sickle cell disease is well known. The interaction between α-thalassemia and sickle cell hemoglobin has been reported extensively in several populations.[3-5] In the Saudi population as early as 1969, Weatherall and coworkers reported the interaction between sickle cell anemia and α-thalassemia as a "new sickling disorder."[6] This is due to the mild nature of the sickle cell genotype in association with α-thalassemia. In the literature, sickle cell anemia is referred to as the homozygous state without other abnormal genes. Once interaction takes place, the clinical condition is often different from the presentation of typical sickle cell anemia.[6-8]

In Saudis, α-thalassemia occurs at a high prevalence. Roberts et al are not up to date in their information on the prevalence of α-thalassemia among the Saudi population in different regions, as they stated that no information is available regarding the prevalence of α-thalassemia in different regions of Saudi Arabia. As early as 1982, α-thalassemia prevalence was reported in different provinces of Saudi Arabia.[9] More recently, using restriction endonucleases, the prevalence of deletion type of α-thalassemia has been determined.[10] Furthermore, the nature of gene deletion, i.e., either leftward or rightward deletion, has been reported in Saudis.[10-13] All studies have clearly shown that α-thalassemia occurs at a high prevalence in Saudis and could be one of the factors that plays a role in amelioration of sickle cell anemia.[14] However, the results from different regions show differences even in regard to the influence of α-thalassemias. Studies in the Southwestern Province show that despite associated α-thalassemia, the disease is not as mild as that reported in the Eastern Province,[15] which has led us to suggest that there are additional factor(s) that play role(s) in amelioration of the sickle cell disease in the Eastern Province.

Roberts et al ought to be aware of the significant differences in the levels of hematologic parameters, particularly total hemoglobin, in male and female adults and children. They have made no attempt to compare the parameter levels and clinical severity in cases with the same age and sex. First, individuals with an overall age range of 1 to 55 years are grouped together. Second, the age range of the patients reported in the paper is significantly different in the different regions and consequently ought to be the hematologic parameters. This would give significant difference, e.g., patients from the Southwestern Province are mainly children, while the patient group from the Eastern Province has a higher number of adults.

Roberts et al reported 13 cases of sickle cell anemia as originating in Riyadh. These patients must have originated from other regions, since the HbS gene frequency is very low in the Central Province,[8] and one hardly encounters sickle cell anemia patients who are originally from this region, and therefore, this study includes a gross misrepresentation of the region. Similarly, in Jeddah, Makkah, and Medina, most, if not all, sickle cell anemia patients must have come from the main foci of the gene.[9]

Roberts et al report indicated that little published information is available on sickle cell disease from parts of Saudi Arabia other than the Eastern Province. This is a serious oversight of several papers on the subject[15-18] where the roles of HbF, G6PD and α-thalassemia were discussed extensively.[14,15]

It would be wrong to say that MCV in the population of eastern Saudi Arabia is lower. It is low as a large proportion had associated α-thalassemia which lowers the MCV. If patients with and without α-thalassemia were separated and the MCV was determined, a higher MCV would be found in SS patients without α-thalassemia.

I cannot understand why there is so much repetition in the figures, e.g., Figures 4 through 7 are all correlating HbF level to age and Figures 5 through 7 are expansions of Figure 4. Similarly, what is shown in the expanded Figures 9 and 10, i.e., correlation between MCV and age, is quite obvious in Figure 8. Are the authors trying to say that age influences MCV level? Without knowing how many patients were iron-deficient or α-thalassemic, such an interpretation is meaningless.

One last point that I would like to raise is regarding the conclusion drawn by Roberts et al. It is quite justified when they say that microcytosis and α-thalassemia lessen severity of sickle cell disease. However, iron deficiency also produces microcytosis. Can the conclusion not be drawn from their results that iron deficiency may be beneficial to patients with sickle cell disease, as it produces microcytosis and may decrease severity? If this were the case, it would suggest that it might be useful therapeutically to induce iron deficiency in patients with sickle cell disease.

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References

1. Roberts GT, El-Badawi SB, Padmos MA, Sackey K. Regional variations in sickle cell anemia in Saudi Arabia. Ann Saudi Med 1988;8(5):320-8.
2. Ganeshaguru K, Omer A, Acquaye J, et al. Clinical significance of serum ferritin. Saudi Med J 1984;5:377-83.
3. Higgs DR, Pressley L, Serjeant GR, Clegg JB, et al. The genetics and molecular basis of alpha-thalassemia in association with Hb S in Jamaican negroes. Br J Haematol 1981;47:43-56.
4. Embury SH, Dozy AM, Miller J, et al. Concurrent sickle cell anemia and α-thalassemia. N Engl J Med 1982;306(5):270-4.
5. Higgs DR, Aldridge BE, Lamb J, et al. The interaction of alpha-thalassemia and homozygous sickle cell disease. N Engl J Med 1982;306:1441-6.
6. Weatherall DJ, Clegg JB, Blackson J, McNeil JR. New sickling disorder resulting from interaction of the genes for haemoglobin S and thalassemia. Br J Haematol 1969;17:517-26.
7. Van Enk A, Lang A, White JM, Lehmann A. Benign obstetric history in women with sickle cell anaemia associated with a-thalassemia. Br Med J 1972;2:524-6.
8. Sewell A, Millard D, Serjeant G. The interaction of alpha-thalassemia with SS disease. In: The red cell. New York: Alan R Liss, 1978:93-102.
9. El-Hazmi MAF. Haemoglobin disorders: a pattern for thalassaemia and haemoglobinopathies in Arabia. Acta Hematol 1982;68:43-51.
10. El-Hazmi MAF. Alpha-thalassemia in Saudi Arabia: deletion pattern. Hum Genet 1987;76:196-8.
11. El-Hazmi MAF. Haemoglobinopathies, thalassemias and enzymopathies in Saudi Arabia: the present status. Acta Hematol 1987;78:130-4.
12. El-Hazmi MAF. Leftward deletion α-thalassemia in the Saudi Arabian population. Hum Genet 1986;74:219-22.

13. El-Hazmi MAF, Warsy AS. Double heterozygote leftward/rightward deletion type alpha-thalassaemia in Saudi Arabs. Hum Hered 1986;36:222-6.
14. El-Hazmi MAF. Clinical manifestation and laboratory findings of sickle cell anaemia in association with α-thalassaemia in Saudi Arabia. Acta Haematol 1985;74:155-60.
15. El-Hazmi MAF, Warsy AS. On the nature of sickle cell disease in the Southwestern Province in Saudi Arabia. Acta Haematol 1986;76:212-6.
16. Babiker MA, Taha SA. Two different patterns of sickle cell disease in children in Saudi Arabia. Ann Trop Paediatr 1982;2:179-81.
17. Babiker MA, El-Hazmi MAF, Al-Jobori AM, et al. Splenic function in children with sickle cell disease: two different patterns in Saudi Arabia. Scand J Haematol 1985;35:191-3.
18. Acquaye JK, Omer A, Ganeshagura K, et al. Non-benign sickle cell anaemia in western Saudi Arabia. Br J Haematol 1985;60:99-108.

To the Editor: With reference to a recent publication by Roberts et al,[1] the authors have provided some additional information on the clinical course of this important disease which affects a large Saudi population. However, they have failed to mention the recent studies done by our group and others.[2-6]

In 1986, we published a paper of similar nature,[2] in which we suggested that α-thalassemia (which causes microcytosis of red blood cells) in association with elevated levels of HbF appears to have a more favorable influence on the clinical course of the disease. It is well known that increased levels of HbF are a feature peculiar to Eastern Province Saudis with sickle cell disease. But it should be mentioned that during our 6-year cord blood screening program,[3,4] we observed outstanding variability in the clinical expression of the disease in our cohort babies who were followed over a length of time, and there was no such threshold level of HbF which protects patients. Differences in HbF levels in Eastern and Western patients with sickle cell disease have been demonstrated by several authors.[5,6] The protective role of HbF is still questionable, as many of our children, even in their first year of life, presented with several clinical manifestations.

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References

1. Roberts GT, El-Badawi SB, Padmos MA, Sackey K. Regional variations in sickle cell anemia in Saudi Arabia. Ann Saudi Med 1988;8(5):320-8.
2. Al-Awamy BH, Niazi GA, El-Mouzan MI, et al. Relationship of hemoglobin F and alpha-thalassemia to severity of sickle cell anemia in the Eastern Province of Saudi Arabia. Ann Trop Paediatr 1986;6:261-5.
3. Al-Awamy BH, El-Mouzan MI, Al-Torki MT, Serjeant GR. Neonatal screening for sickle cell disease in the Eastern Province of Saudi Arabia. Trans R Soc Trop Med Hyg 1984;78:792-4.
4. Al-Awamy BH, Niazi GA, El-Mouzan MI, et al. Newborn screening for sickle cell hemoglobinopathy and other inherited erythrocytic disorders in the Eastern Province of Saudi Arabia. Saudi Med J 1986;7:502-9.
5. El-Hazmi MAF. Clinical manifestation and laboratory findings of sickle cell anaemia in association with α-thalassemia in Saudi Arabia. Acta Haematol 1985;74:155-60.
6. Al-Awamy BH, Naeem MA. Splenic and hepatic function in sickle cell anemia with special emphasis on patients from the Eastern Province of Saudi Arabia. Saudi Med J 1986;7:434-42.

The above letters were referred to the authors of the article in question, who offer the following reply:

The point of our article was to show that there could be regional variation in some of the clinical and hematologic manifestations of sickle cell disease in Saudi Arabia, which may be related to, among other factors, varying prevalence of α-thalassemia in the different regions. One of the central points in the paper was the fact that microcytosis was a common feature in SS patients, and as stated in the paper, this could be due to either interaction with β-thalassemia or α-thalassemia genes. We excluded a number of patients with microcytosis in whom, by family study (a highly reliable method of genetic analysis), we could not exclude sickle cell β-thalassemia. Thus, we considered that the remainder were true homozygous SS patients without the interaction of a β-thalassemia gene. The problem then revolved around whether some patients had interacting α-thalassemia or not. The group with normal MCV, that is, MCV greater than 80 fL, were considered not likely to have an interacting α-thalassemia gene, and those with MCV of less than 80 fL were considered likely to have an interacting α-thalassemia gene. However, this analysis was confounded by the fact that iron deficiency could have played a part in reducing the MCV. We stated this in the Methods section, but because the study was retrospective, iron studies were not uniformly available. Instead we used the device of comparing the MCV in women of childbearing age who were likely to be iron deficient with that of men and could show no difference. This suggested that iron deficiency was not likely to be present in our group of patients. El-Hazmi's own unpublished ancedotal observations of iron deficiency among his patients are interesting, but do not constitute evidence that iron deficiency is a *common* finding in patients with SS in Saudi Arabia, although we admit that iron deficiency is known to occur among patients with SS or sickle cell/hemoglobin C (SC) disease. This was observed in a restricted study of 22 pregnant and 18 nonpregnant SS and SC women in the Ibadan area of Nigeria.[1] In another even more restricted study of four patients, three females and one male had overt bleeding which led to iron-deficiency anemia.[2] The study from Western Saudi Arabia by Ganeshaguru et al,[3] showing iron sufficiency among their patients with sickle cell disease, is supported by a previous (small) study by Fleming, again from the Ibadan area.[4] In any event, we have reviewed the serum iron and total iron-binding capacities done on 30 (37%) of our patients and could find no patients with a transferrin saturation of less than 30%. None of the 81 patients had overt bleeding.

We recognize the high prevalence of α-thalassemia in certain populations in Saudi Arabia,[5] but it is also true that information on the various manifestations of SS, as affected by α-thalassemia, is scanty for the Kingdom as a whole. We discussed these interactions extensively in the article. A number of the relevant citations[6,7] quoted by El-Hazmi were included in this discussion, but others, not included, also provide support for our view that the clinical manifestations of the disease could vary within the Kingdom.[8] This variation we postulate may be partly attributable to a varying prevalence of α-thalassemia which may result in the lowering of the average MCV in the populations studied. Those patients without α-thalassemia or β-thalassemia genes are likely to have higher MCVs and may have more severe manifestations of the disease.

The differences in hematological parameters associated with age and sex are appreciated, but our cutoff point of 100 g/L for hemoglobin is considered valid for all age groups and both sexes, based on published normal reference ranges from various regions of Saudi Arabia.[9-12]

We have considered the possible effect of microcytosis induced by iron deficiency on the severity of SS and agree that, a priori, it could be beneficial. However, experience with the rheological changes in polycythemia rubra patients made iron deficient by repeated phlebotomy urges caution.[13,14] A study examining the rheological changes in iron-deficient SS patients would be helpful in determining a rational approach, and perhaps El-Hazmi's iron-deficient SS patients could serve as a starting point for such a study.

We believe that the final word on sickle cell disease in Saudi Arabia, or indeed in any other geographic area, has not yet been written and information from all quarters would certainly be useful in further understanding of this complex disease.

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References

1. Oluboyede OA. Iron studies in pregnant and non-pregnant women with hemoglobin SS or SC disease. Br J Obstet Gynaecol 1980;87:989-96.
2. Haddy TB, Castro O. Overt iron deficiency in sickle cell disease. Arch Intern Med 1982;142:1621-4.
3. Ganeshaguru K, Omer A, Acquaye J, et al. Clinical significance of serum ferritin. Saudi Med J 1984;5:377-83.
4. Fleming AF. Iron status of anaemic pregnant Nigerian. J Obstet Gynaecol Br Comm 1969;76:1013-7.
5. Pembrey ME, Weatherall DJ, Clegg JB, et al. Hemoglobin Bart's in Saudi Arabia. Br J Haematol 1975;29:221-34.
6. Higgs DR, Aldridge BE, Lamb J, et al. The interaction of alpha-thalassemia and homozygous sickle cell disease. N Engl J Med 1982;306:1441-6.
7. Embury SH, Dozy AM, Miller J, et al. Concurrent sickle cell anemia and alpha-thalassemia: effects on severity of anemia. N Engl J Med 1982;306(5):270-4.

8. Weatherall DJ, Clegg JB, Blackson J, McNeil JR. New sickling disorder resulting from interaction of the genes for haemoglobin S and thalassaemia. Br J Haematol 1969;17:517-26.
9. Scott TG. A pilot study of the reference values for the commoner haematological and biochemical parameters in Saudi nationals. J Clin Pathol 1982;35:59-73.
10. Roberts GT, El-Badawi SB. Red blood cell distribution width index in some hematological disease. Am J Clin Pathol 1985;83:222-6.
11. Bacchus R, Garner E, Madkour MM, et al. The haematology reference range for Saudi Arabians. Saudi Med J 1986;7:46-52.
12. Ghafouri HN, Al-Fares AM, Islam SI, et al. Haematological reference values from birth to adolescence in Saudi subjects in the area of Jeddah. Saudi Med J 1987;575-82.
13. Hutton RD. The effects of iron deficiency on whole blood viscosity in polycythaemic patients. Br J Haematol 1979;43:191-9.
14. Milligan DW, MacNamee R, Roberts BE, Davies JA. The influence of iron deficiency on whole blood viscosity in polycythaemia. Br J Haematol 1982;50:467-73.

Intracranial Neoplasms Among Arabs

To the Editor: Dr. Jamjoom is to be commended for his meticulous and detailed study of the pattern of intracranial space-occupying lesions in Saudi Arabia.[1] The comparative data he presented in the discussion have been thoroughly researched, particularly regarding the variations in the relative frequency of various intracranial neoplasms in Saudi Arabia and many Asian, African, and Western countries.

I would like to add a few personal observations based on my experience as a pathologist in a review of 400 intracranial neoplasms in Jordanian patients,[2] as well as the observations of other Arab workers from Syria,[3] Lebanon,[4] and Egypt,[5] so as to complement Dr. Jamjoom's study by adding data on the frequency of intracranial space-occupying lesions in neighboring Arab countries.

Table 1 shows the distribution of brain tumors in five Arab countries including Saudi Arabia. Jordan has the highest frequency of gliomas, and this could be due to inclusion of nonneoplastic conditions in the other series.

Saudi Arabia and Egypt have the highest frequency of meningiomas. The remaining types of intracranial tumors are closely similar in distribution with the exception of pituitary adenomas, which are frequently observed in the Syrian and Saudi series. Metastatic tumors show some variations from one series to another, depending on how far the neurosurgeons are willing to excise metastatic deposits in the brain. It should be stated that the Arab series are based on surgically removed material or clinically diagnosed cases

TABLE 1. *Intracranial space-occupying lesions (%) in Arabs.*

Country	No. of cases	Gliomas	Meningiomas	Acoustic neuromas	Pituitary adenomas	Vascular tumors and malformation	Congenital and malformative tumors	Metastatic tumors	Others
Syria, 1950–65[3]	300	45	16	3	16	2	0.5	2	8.5
Lebanon, 1955–68[4]	626	47.1	16.2	3	3.5	2.3	3.6	6.8	17.5
Egypt, 1956–62[5]	377	40.8	19.8	7.2	3.4	3.4	5.1	3.7	11.6
Egypt, 1966–70[5]	291	47.5	28.3	2.1	5.2	4.2	4.9	2.1	7.9
Jordan, 1976–83[2]*	400	56.6	22.5	2.8	7.3	2.7	4.2	2.3	1.7
Saudi Arabia, 1982–87[1]	212	39.7	22.8	3.8	16.8	2.7	4.3	8.2	1.7
Saudi Arabia, 1982–87[1]*†	120	40	28.3	3.4	13.3	1.7	5.8	6.7	0.8

* Intracranial neoplasms only.
† Saudi nationals only.

TABLE 2. *Comparison of gliomas in Saudi Arabia and Jordan.*

	Saudi Arabia	Jordan
Histologic type	No. (%)	No. (%)
Astrocytoma, grades I and II (benign astrocytomas)	11 (15.1)	80 (35.4)
Astrocytoma, grades III and IV (malignant astrocytomas and glioblastoma multiforme)	30 (41.1)	87 (38.5)
Medulloblastoma	7 (9.6)	30 (13.3)
Ependymoma	5 (6.8)	8 (3.5)
Oligodendroglioma	1 (1.4)	9 (4.0)
Spongioblastoma	1 (1.4)	0
Ganglioglioma	0	1 (0.4)
Ganglioneuroma	0	1 (0.4)
Mixed glioma	0	8 (3.5)
Choroid plexus papilloma	0	2 (0.9)
Unspecified	18 (24.6)	0
Total	73	226

and do not include autopsy material.

Acoustic neuromas (nerve-sheath cell tumors) have a high frequency in Asian countries, moderate occurrence in Western countries, and low frequency in Arabs in general. Congenital and malformative tumors are less frequent in Arabs than in Far East Asians who have the highest incidence of these neoplasms. The Japanese have also the highest frequency of pinelomas, which are rare in the Saudi study (one case)[1] and absent in the Jordanian series.[2]

On comparing various types of gliomas (neuroepithelial tumors) in Saudi Arabia and Jordan, some differences in the distribution of these neoplasms are noted (Table 2). Both studies used WHO classification of brain tumors and Kernohan's system for grading astrocytomas. Grades I and II were considered as benign astrocytomas while grades III and IV were considered malignant. In the Jordanian study, there were 37 cases which were considered as glioblastoma multiforme based on WHO histologic criteria, and these were added to high-grade astrocytomas in Table 2. Apparently, glioblastoma multiforme was incorporated with high-grade (malignant) astrocytomas in the Saudi series.

More studies on various types of intracranial space-occupying lesions in the Arab countries are needed for better understanding their clinical presentation, behavior, methods of diagnosis, and outcome of available modalities of treatment.

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References

1. Jamjoom ZAB. Pattern of intracranial space-occupying lesions: the experience of the King Khalid University Hospital. Ann Saudi Med 1989;9(1):3-10.
2. Amr SS, Jitawi Sa, Maraqa IA, et al. Intracranial neoplasms in Jordan: a pathological study of 400 cases. Jordan Med J 1986;20(1):67-80.
3. Sabbagh F. Brain tumors in Syria. In: Proceedings of the sixth scientific week, third book: Studies and researches in medical sciences, Damascus, 4-9 December 1965. Syrian Arab Republic, Higher Council for Science, 1966;213 (in Arabic).
4. Haddad F. Reflections on the first 626 craniotomies of brain tumors carried out in Beirut. In: Proceedings of the ninth scientific week, third book: Studies and researches in medical sciences, Damascus, 9-14 November 1968. Syrian Arab Republic, Higher Council for Science, 1969:65.
5. Sorour O, Rifaat M, Lofti M. The relative frequency of brain tumors in Egypt. Afr J Med Sci 1973;4(2):179-86.

So-Called Endometrioid Adenocarcinoma of the Prostate: A Misnomer

To the Editor: Since the first description of endometrial carcinoma of the prostatic utricle,[1] a suggestive hypothesis was made about the histogenesis of some prostatic adenocarcinomas showing endometrioid features. The arrival of an immunohistochemical method as a practical diagnostic tool was the end of this attractive idea. I have recently observed a case of papillary adenocarcinoma arising within the prostate gland closely related with the urethra, and some old and recent questions came to my mind.

The patient was a 66-year-old man with urinary retention syndrome and macroscopic hematuria noticed several months before. On cystoscopic examination, an obstructive mass pushing the urethral wall was observed around the verumontanum. Findings on rectal examination were normal. Serum acid phosphatase and other biochemical determinations were within normal limits. Transurethral resection was done, and the patient was symptom-free 1 year later.

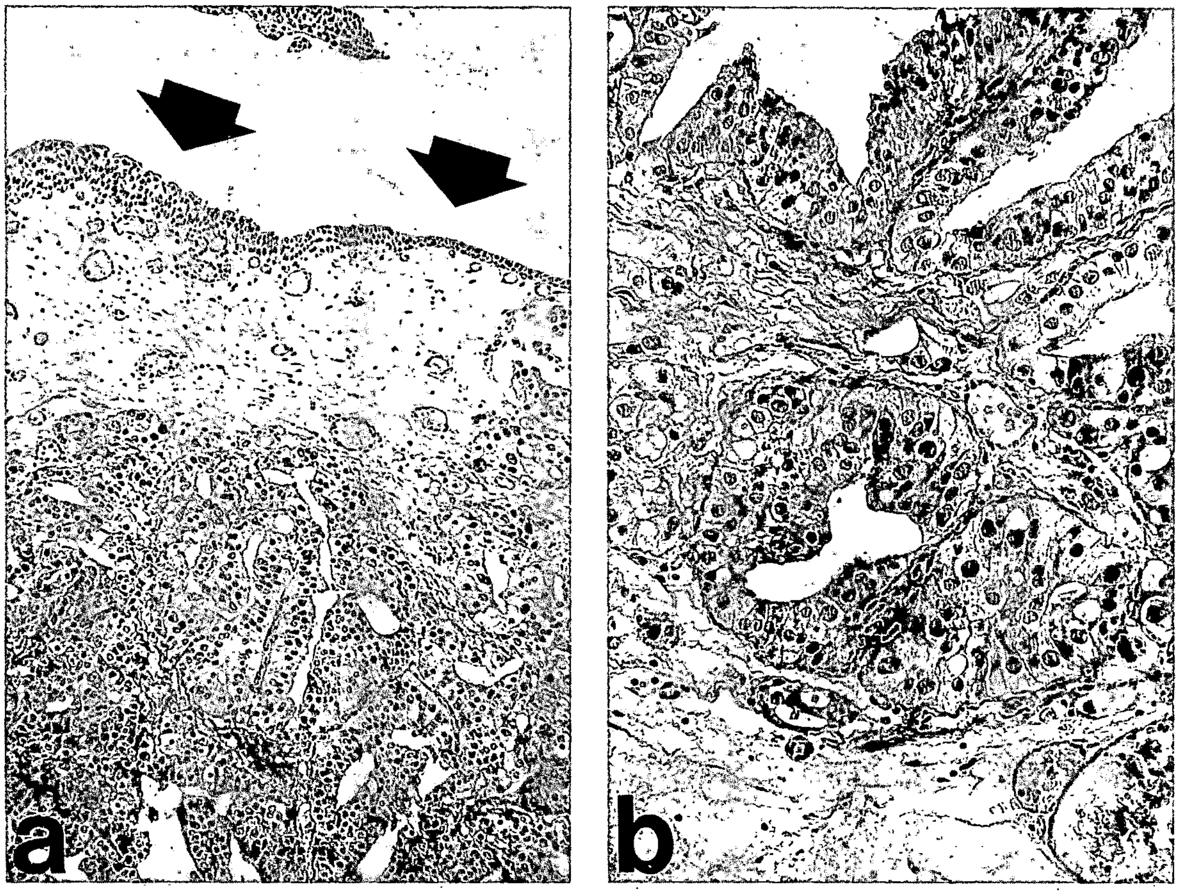

FIGURE 1. (a) panoramic view illustrating the neoplastic growth beneath the urothelium (arrows) (hematoxylin and eosin, original magnification, ×100). (b) tubulopapillary pattern lined by tall columnar neoplastic cells (hematoxylin and eosin, original magnification, ×400).

Histopathologic examination (Figure 1) of the surgical specimen showed a neoplastic growth beneath the urothelium with a prominent papillary pattern. Papillae were composed of tall columnar pseudostratified cells with abundant eosinophilic cytoplasms. Occasionally, a tubular pattern with back-to-back features was observed, mainly at the edge of the tumor. Mild atypia and mitosis were present. Prostatic-specific antigen resulted in a positive cytoplasmic stain.

Prostatic adenocarcinomas with prominent papillary pattern are infrequent.[2] A suggestive hypothesis concerning mullerian origin has been proposed.[1,3] This hypothesis was based on the histologic similarities with endometrial carcinoma. Moreover, a typical localization closely related with the utriculum prostaticum—a proved mullerian structure—was claimed as additional proof. On the other hand, some authors[4] advocated a prostatic duct origin and supported it with ultrastructural studies. More recently, some ultrastructural studies[5,6] confirmed those findings. Since immunohistochemical reports[2,5,7,8] identify both prostatic specific antigen and prostatic acid phosphatase in those tumors—both are not demonstrated in endometrial carcinoma—the controversy seems to have been clarified.

In summary, the so-called endometrioid adenocarcinoma of the prostate is a misnomer leading to confusion, and it should be abandoned. Prostatic ducts are the most reasonable origin of this entity, and the papillary pattern must be interpreted as an architectural variant.

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References

1. Melicow MM, Pachter MR. Endometrial carcinoma of prostatic utricle (uterus masculinus). Cancer 1967;20:1715-22.
2. Epstein JI, Woodruff JM. Adenocarcinoma of the prostate with endometrioid features: a light microscopic and immunohistochemical study of ten cases. Cancer 1986;57:111-9.
3. Melicow MM, Tannenbaum M. Endometrial carcinoma of the uterus masculinus (prostatic utricle): report of six cases. J Urol 1971;106:892-902.
4. Zaluodek C, Williams JW, Kempson RL. Endometrial adenocarcinoma of the prostate: a distinctive tumor of probable prostatic duct origin. Cancer 1976;37:2255-62.
5. Bostwick DG, Kindrachuk RW, Rouse RV. Prostatic adenocarcinoma with endometrioid features: clinical, pathologic, and ultrastructural findings. Am J Surg Pathol 1985;9:595-609.
6. Srigley JR, Hartwick WJ, Edwards V, DeHarven E. Selected ultrastructural aspects of urothelial and prostatic tumors. Ultrastruct Pathol 1988;12:67-86.
7. Nadji M, Tabei SZ, Castro A, et al. Prostatic origin of tumors, an immunohistochemical study. Am J Clin Pathol 1980;73:735-9.
8. Walker AN, Mills SE, Fechner RE, Perry JM. Endometrial adenocarcinoma of the prostatic urethra arising in a villous polyp: a light microscopic and immunoperoxidase study. Arch Pathol Lab Med 1982;106:624-7.

Traumatic Tracheoesophageal Fistula

To the Editor: Traumatic tracheoesophageal fistula is very rare compared to the congenital variety. We have treated a 3-year-old boy in whom traumatic tracheoesophageal fistula developed after he swallowed the pullring and tab of a soft drink container. The pull tab became adherent to the proximal esophagus, which it subsequently perforated, creating an esophageal abscess. The abscess perforated the trachea, and a traumatic tracheoesophageal fistula developed. The pull tab was too large to be aspirated via the trachea, but rather, it was swallowed into the esophagus and found its way to the trachea.

The patient had no symptoms for 6 months until respiratory distress and recurrent pneumonia developed. The foreign body was overlooked on initial chest and neck x-ray films, but further review revealed the foreign body in the cervical area (Figure 1).

After diagnosis, the foreign body was removed and the fistula repaired, but multiple surgical procedures were required, and hospitalization was lengthy. The patient recovered completely.

Detachable pull tabs on drink cans are illegal in most Western countries, but are still available in Saudi Arabia. We believe this unfortunate incident could have been prevented, and we urge banning the present type of soft drink container. We advocate the use of soft drink containers with nondetachable flip-top tabs.

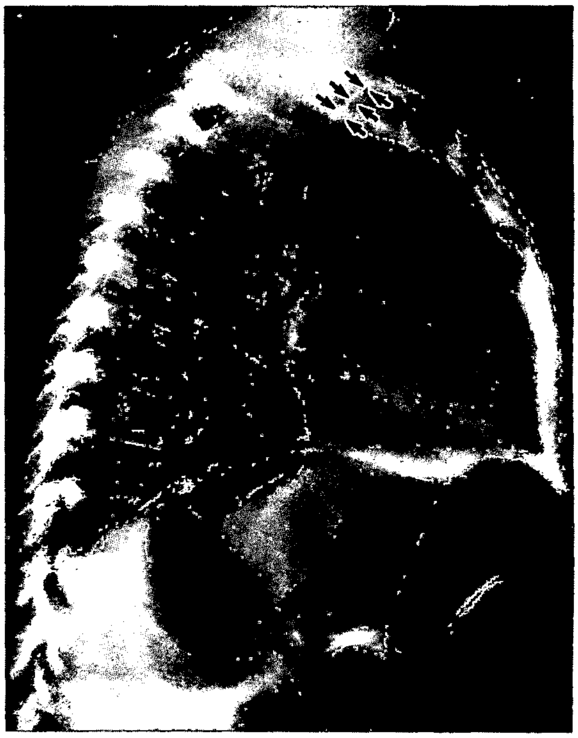
FIGURE 1. Lateral chest x-ray film showing the pull tab in the cervical area between arrows.

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Cholecystectomy Without Drainage

To the Editor: The prospective randomized study, "Cholecystectomy without drainage," by Latif et al[1] is quite convincing. We had favored, as early as 1954, closure of the peritoneum without drainage after cholecystectomy. No drainage was used in

78% of patients with chronic cholecystitis and/or cholelithiasis and in only 18% of patients suffering from acute cholecystitis.[2,3] Despite this early clinical experience, the question whether to drain or not to drain remained open in 1985, at least for some.[4] The authors very elegantly and conclusively prove the point that no drain resulted in a significantly shorter hospital stay and a lower rate of subjective discomfort in uncomplicated cholecystectomy. Sixteen patients out of a total of 116, i.e., 14%, were excluded from the study because they had diabetes, jaundice, empyema or pericholecystic abscess; in other words, 86% of the patients were considered possible candidates for the no-drain closure, even those with uncomplicated acute cholecystitis. Our indication for the no-drain closure could be summarized as a clean and dry operative field.[2] We also did away with the routine use of the nasogastric tube; we did not use it in any of our 155 cholecystectomy cases.[2,3]

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References

1. Latif AA, Hussain SA, Choudhary A, Al-Saigh A. Cholecystectomy without drainage: a controlled clinical trial. Ann Saudi Med 1989;9(1):36-8.
2. Haddad FS. Gall bladder disease. Ann Rep Orient Hosp 1955;8:4-7.
3. Haddad FS, Haddad SI. Gall bladder disease. Ann Rep Orient Hosp 1963;16:1179-88.
4. Hoffmann J, Lorentzen M. Drainage after cholecystectomy. Br J Surg 1985;72:423-7.

Familial Mediterranean Fever Among Arabs

To the Editor: I read with interest the letter to the editor by Dr. Fahim describing two Yemeni patients affected with familial Mediterranean fever (FMF),[1] and I would like to comment on a few statements made in that letter.

Many Arab patients with FMF had been reported, and several of them were from the Arabian peninsula. Abdul Ghaffar reported on 418 patients with FMF whom he treated between 1944 and 1974 with a variety of therapeutic regimens.[2] Of 418 patients, 369 were Egyptian, while the remaining 49 came from other Arab countries, namely, Jordan, Syria, Lebanon, Saudi Arabia, Bahrain, Qatar, Sudan, Iraq, Kuwait, and Algeria. Wahib et al reported 20 patients with FMF they treated during the period 1982-1984 at Buraydah Central Hospital in the Qassim Province, Saudi Arabia.[3] Fourteen of these patients were Saudi Arabs, and two patients each were from Egypt, Sudan, and Jordan. More recently, Barakat et al,[4] in an elaborate detailed study of 175 Arab patients with FMF residing in Kuwait, found their patients to originate from Palestine (64%), Egypt (14.9%), Lebanon (9.7%), Syria (7.4%), and Iraq (4%). No native Kuwaitis were found in the whole series. Several reports on FMF came from Lebanon, and the largest series from the country reported 120 patients.[5]

The frequency of renal amyloidosis in Arab patients affected by FMF is variable from one study to another but is not exceedingly rare as had been stated.[1] In a study from Lebanon, nine of 120 patients (7.5%) with FMF had amyloidosis.[5] However, only three patients (1.7%) revealed evidence of amyloidosis in the series from Kuwait.[4] In a study of 20 patients with renal amyloidosis from Jordan, five were affected with FMF.[6]

More work is needed to delineate FMF in the Arab countries and its association with renal amyloidosis, which is the most notable cause of death in patients with FMF.

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References

1. Fahim AS. Familial Mediterranean fever in Yemen Arab Republic. Ann Saudi Med 1988;8(6):512-3.
2. Abdul Ghaffar Y. Therapeutic trials in familial Mediterranean fever. Ain Shams Med J 1974;25(6):741-4.
3. Wahib AA, El-Naggar MK, Montasser MF, et al. Familial Mediterranean fever in Saudi Arabia. J Egypt Med Assoc 1984;67(suppl 3):71-6.
4. Barakat MH, Karnik AM, Majeed HWA, et al. Familial Mediterranean fever (recurrent hereditary polyserositis) in Arabs: a study of 175 patients and review of the literature. Q J Med 1986;60(233):837-47.
5. Armenian HK, Khachadurian AK. Familial paroxysmal polyserositis: clinical and laboratory findings in 120 cases. Lab Med J 1973;26(6):605-14.
6. Amr SS, Hamzeh YS. Renal amyloidosis in Jordan. Trop Geogr Med 1985;37(2):167-70.

SECOND SYMPOSIUM ON BURNS AND PLASTIC SURGERY

Sponsored by the Joint Board for Postgraduate Medical Education
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13-14 Rabi Al-Awal 1409 (23-24 October 1988)

AN EPIDEMIOLOGICAL SURVEY OF BURNS IN CHILDHOOD IN SAUDI ARABIA, AR Al-Bunyan, Riyadh Central Hospital

An epidemiological survey of burns in children in Saudi Arabia was conducted for the 4 years 1404-1407H. It brought out some useful information, which can be of practical value in reducing the incidence and morbidity and mortality. The incidence was highest among toddlers, scalds were commonest type of burn injury in children, the depth of burns was less in patients treated by pouring cold water on the burned area immediately after sustaining the burn, and the mortality and morbidity were less in patients who received hospital treatment from the start.

MUTILATING INJURIES OF THE HAND BY A MEAT MINCER, E Cardoso, MT Husain, P Kumar, J Hassanain, King Khalid University Hospital, Riyadh.

Power machines are responsible for the majority of mutilating injuries of the hand in industrially advanced as well as developing countries. With modernization, the power-driven tools have made rapid headway in the domestic arena. Failure to recognize the risks involved in the use of such appliances has become a hazard, particularly to the junior members of the household, resulting in disastrous consequences. We reported here our experience with 19 consecutive cases (14 children and 5 adults) of meat-mincer injuries of the hand treated in King Khalid University Hospital, Riyadh, from January 1985 to July 1988. The pattern of injury to the hand, the extent of damage to individual fingers and the results of treatment were analyzed. Safety measures to prevent these fatal and disabling injuries, which occur with great frequency in the Kingdom, were emphasized.

BURN SERVICE: PAST, PRESENT, AND FUTURE IN SAUDI ARABIA, DM Diab, Riyadh Armed Forces Hospital

The surface area of Saudi Arabia is equal to the whole of Europe except France. With this vast amount of surface area it is extremely difficult to centralize a national burn service. Accordingly, each province has planned its own facilities to care for burn patients. A survey was done to look at the burn units available in Saudi Arabia at present and the plans in the coming 18 months. At present there are 14 burn units with another three planned in the coming 18 months. The total number of beds available now is 145. The actual number of active beds is 63. The military service represents 43%. The three units under construction are to replace other beds which do not satisfy the purpose-built burn unit. Out of this total number, five burn units belong to the military service, and in 18 months' time, the military service will have 48% of the total number of beds in Saudi Arabia. By 18 months' time, the facility for burn patients in Saudi Arabia will exceed the Western international standard in physical plan. The main problem is staffing the purpose-built burn unit. About 34 fully trained consultants and senior registrars are needed in addition to 68 junior staff in training. This is not to mention the expert nursing and paramedical staff. In conclusion, burns are better to be prevented than treated, but for those unfortunate burn patients, an excellent facility will be available in the Kingdom to match the Western international standard in the coming 18 months. Our local medical, paramedical, and nursing staffs have to be encouraged to join this demanding subspecialty service.

HISTORY OF PLASTIC SURGERY IN SAUDI ARABIA: 1324 OPERATIONS FOR 883 PATIENTS WITH CLEFT LIP AND PALATE IN 13 YEARS, DM Diab, Riyadh Armed Forces Hospital

The incidence of cleft lip and palate has been established in Saudi Arabia as occurring in one in 1253 live-born infants. This is based on reviewing 29,052 live-born infants in 7 years. The following results summarize a small series at Riyadh Armed Forces Hospital in the last 3 years comprising 124 operations for 83 patients. Sixteen percent were referred to RAFH after surgery elsewhere for revision: all cleft palate repairs were done with Von Langenbeck technique. Only three pharyngeal flaps were done for improvement of speech; the successful result of one-shot surgery for a cleft palate was 94% — for cleft lip straight line, 7.2%; quadrilateral flap, 8.6%; triangular, 18.8%; Millard repair, 65.2%. The technique was chosen to fit each patient.

INTRODUCTION TO THE BALLISTICS OF GUNSHOT WOUNDS, METALLIC FRAGMENT WOUNDS, AND BLAST WOUNDS OF THE MAXILLOFACIAL REGION, G Hennig, King Fahad National Guard Hospital, Riyadh

The knowledge of etiology of disease and injury greatly determines the methodology, course, and outcome of treatment rendered. In the case of gunshot wounds, metallic fragment wounds, and blast wounds, it is important for the surgeon who is to assess and treat the victims of such injuries to have a basic understanding of the ballistics underlying gunshot, metallic, and other fragment wounds. Extent of injuries, treatment regimens, and treatment outcome vary greatly depending on the type of the missile/bullet or fragment, the velocity, and the mass of the injuring agent. It was the purpose of this presentation to provide a simple but correct explanation of wound ballistics and delineation of the immediate treatment of maxillofacial gunshot, fragment, and blast wounds.

AN ANALYSIS OF INFECTION IN A BURN WARD, MT Husain, QN Karim, S Tajuri, King Khalid University Hospital, Riyadh

A total of 172 burn wound swabs obtained from 90 patients admitted to the Aljalal Hospital Burn Unit, Benghazi, over a 5-month period were processed to determine the microbial flora colonizing burns and their resistance patterns to selected locally available topical and systemic agents. Approximately 85% of the swab specimens yielded growth of 11 bacterial genera and *Candida* spp; of these, *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Klebsiella* spp. predominated in order of prevalence, followed by enterobacteria. Polymyxin (100%), amikacin (91%), and carbenicillin (67%) were the most effective of 10 selected antibiotics tested against the 60 *Pseudomonas* isolates. In in vitro studies using six topical agents, *P. aeruginosa* strains were most sensitive, in decreasing order, to mafenide acetate, silver sulfadiazine, acetic acid, silver nitrate, and Eusol. Seventy-eight percent of *S. aureus* isolates were resistant to methicillin and erythromycin and 93% to tetracycline.

BURIED PENIS IN ARAB CHILDREN, MT Husain, A Al-Samarrai, E Cardoso, P Kumar, J Hasanain, King Khalid University Hospital, Riyadh

Webbed penis is a rare congenital anomaly. Only 29 cases have been reported in the literature so far. Only one of these was an Egyptian child. We have reported four more cases; two Saudi babies and two Libyan babies. The literature was reviewed and a new classification has been suggested. Methods of management were discussed.

SULFURIC ACID BURN: A MASS DOMESTIC ACCIDENT, JM Hassanain, MT Husain, E Cardoso, P Kumar, King Khalid University Hospital, Riyadh

Most of the sulfuric acid burns reported are either industrial accidents or acts of vengence, and most of them are usually smaller burns. Similarly, most of these burns are in adults. We had the misfortune of treating six children as a result of a single domestic accident, one with 60% burn, one with 7%, and the rest smaller areas. The problems faced in extensive acid burns and their management were discussed and illustrated with our cases.

REPLANTATION AND REVASCULARIZATION OF POST-TRAUMATIC LIMB AMPUTATIONS AT KING KHALID UNIVERSITY HOSPITAL, RIYADH, P Kumar, MT Hussain, E Cardoso, J Hassanain, King Khalid University Hospital, Riyadh

With the advances in microvascular surgery, the replantation of the amputated parts has become an established treatment modality all over the world. At King Khalid University Hospital, Riyadh, replantation and revascularization surgery was started in April 1984. This is a preliminary review of the cases performed between April 1984 and April 1988. Altogether, 70 patients were referred during this period. Out of these, 34 cases were not suitable for attempting replantation surgery due to various reasons. In the other 36 patients, replantation or revascularization was attempted on a total of 46 units. Our net survival rate was 67.4%. An analysis of these cases was done to study the type of patients involved, nature of injuries, and methods of management. The data were presented, discussed, and compared with other published series.

THE BURNS OF UPPER EXTREMITY: A CHALLENGE FOR PHYSIOTHERAPIST, D Mathur, Sabya General Hospital, Sabya, Gizan

Next to the brain, the upper extremity is the body's greatest asset, and as such, the upper extremity needs particular attention. It must be kept in good functional condition. After the surgeon's immediate care, whatever the extent of burn that the patient has sustained, care of the chest must be the first consideration of the physiotherapist. The most important factor in any case of burn is shock during this stage; there is a lack of spontaneous cough and mobility, and the patient with depressed level of consciousness may have excessive secretion retention. Therefore, chest physiotherapy plays an important role. Chest physiotherapy includes four maneuvers: (1) postural drainage, (2) coughing, (3) suctioning, and (4) breathing exercises in spontaneously breathing patients. General principles of physiotherapy in patients with upper extremity burns are to restore function and to prevent skin hardening. Burns are particularly liable to the formation of hard keloid scars, which besides disfigurement, lead to contracture and deformity. There will inevitably be some shrinking of the scar tissue when burns repair naturally. This can lead to terrible contracture and deformity if physiotherapy is not carried out properly and promptly.

MICROSURGICAL RECONSTRUCTION OF SEVERE UPPER LIMB INJURIES, JM Pitkanen, Almujammaa Attebbi Alaskari, Dhahran

Early soft tissue coverage of vital structures like vascular bundles, nerves, tendons, and bone is essential to minimize the effect of the trauma and prevent amputations. In a series of 10 cases of severe upper limb traumas, early soft tissue coverage was achieved with microsurgical transfers of musculocutaneous and fasciocutaneous flaps with salvage of length and function of the limb. In this series there was no flap loss. The different microsurgical flaps used, follow-up results, and the advantages/disadvantages of the procedures were discussed.

AN OPERATIVE TECHNIQUE FOR CORRECTION OF CONGENITAL GIGANTISM OF THE TOES, SS Rawat, Riyadh Central Hospital

An operative technique has been described for the correction of congenital gigantism of the toes. The operation is applicable to gigantism of different local causes, i.e., neurofibroma, hemangioma, lymphangioma, and diffuse hypertrophy of the fibrofatty tissue. The technique consists of excising proximal or proximal and middle phalanges along with the surrounding soft tissues, keeping intact the neurovascular bundles on both sides. The distal stumps are telescoped proximally.

ORTHODONTIC MANAGEMENT OF CLEFT LIP AND PALATE, IA Nashashibi, College of Dentistry, King Saud University, Riyadh

Clefts of the lip and palate produce physical, physiological, and emotional disturbances in patients and hinder the growth pattern of the craniofacial complex which resulted in the retropositioning of the maxilla and the mandible relative to the anterior cranial base. Growth is thought to be normal in the horizontal direction but not in the vertical direction. The nasal septum is always deviated to the noncleft side. Surgical repair of the palate and the scar tissue prevents the normal process of expansion of the growing structures. Three stages of orthodontic treatment have been designed. The first treatment usually starts 48 hours after birth by preparing the presurgical orthopedic treatment; the second stage of treatment at the age of 7 to 8$^1/_2$ years. Only minor orthodontic treatment must be carried out to correct crossbites. The third stage of treatment is usually undertaken when all the permanent teeth have fully erupted.

MULTIPLE SEBACEOUS CYSTS OF THE SCROTUM WITH CALCIFICATION, SS Rawat, Riyadh Central Hospital

The author has recently treated and studied nine cases of nodular calcification of the scrotum. Multiple calcification of the scrotum has been frequently reported. Different types of scrotal calcification have been reported. Recently an entity, idiopathic calcinosis of the scrotum, has been described. Our study indicates that they are really cases of calcification of the sebaceous cysts. We have in our series cases of sebaceous cysts without calcification, cases where only some of the cysts are calcified, and cases where there are only calcified nodes without any evidence of sebaceous cysts. However, the histologic features of the two latter types of cases are identical.

ACUTE MANAGEMENT OF BURNS IN INFANTS AND CHILDREN, Z Skef, Security Forces Hospital, Riyadh

Burns are common among Saudi children, and 85% of such injuries are potentially preventable. Scald burns are more common under 3 years of age, and they affect boys twice as often as girls. Scald burns are the most common cause of minor burns in children. Although scald injuries result in a partial-thickness skin loss, a full-thickness skin injury does occur in infants and young children because of the thinness of their skin. Flame burns are more common over 3 years of age, with equal sex predilection. Flammable fabrics still are involved in over 60% of the incidents. The main problems associated with minor partial-thickness burns ($< 15\%$ body surface) are pain, superficial infection, wound drainage, prolonged convalescence, and scarring. A simple and conservative approach to the treatment of these burns is essential in achieving good results. Management of major burns in infants and small children requires special care. There is a great disparity in surface area as related to body weight in a young child in comparison to an adult. This would mean a major metabolic difference (water evaporation rate, heat and water loss, caloric needs, etc.). A comprehensive approach to the acute care of burned children would include an initial evaluation, airway management, nasogastric drainage, adequate fluid and electrolyte therapy, nutritional support, wound care and coverage, an active physiotherapy program, and adequate support to the child and his family until he achieves full rehabilitation. A review of all aspects of acute care of a burn injured child was presented.

CLOSURE OF ABDOMINAL WALL DEFECT IN INFANTS, Z Skef, Security Forces Hospital, Riyadh

Small abdominal wall defects are easily managed in infants. Large defects pose a challenging problem which requires a well-planned program of surgical and medical therapy on which the infants' life could depend. The anterior abdominal wall develops by lateral infolding and ventral flexion of the trilaminar disk-shaped embryo in the fourth week of life, accompanied by the ventral migration of mesoderm. The cephalic, caudal, and lateral folds are each composed of somatic and splanchnic layers. Early failure of formation of the somatic layer of the cephalic fold causes an underlying epigastric abdominal wall defect. Caudal fold failure of normal formation leads to a lower abdominal wall defect. This could include some hindgut anomalies, while failure of foldings and fusion of the lateral folds results in an umbilical ring which remains widely open. A thorough knowledge of the abdominal wall embryology and anatomy is essential. A variety of surgical techniques have been available in the past. Newer techniques of myocutaneous flaps have been most helpful. We described our experience in dealing with a variety of infants with abdominal wall defects, their surgical management, methods used, and outcome.

FUNGAL COLONIZATION OF BURN WOUNDS, S Tajuri, MT Husain, A Malik, Arab Medical University, Benghazi, Libya

Since the advent of local chemoprophylaxis, there has been a decline in bacterial wound sepsis, but parallel to it has been increasing incidence of fungal infection with resultant morbidity and mortality. A prospective study was undertaken to determine the incidence of fungal colonization of burn wounds and to detect the probable source. Seventy patients were studied during the study. All had prophylactic Ampiclox and local antibacterial prophylaxis. Overall 60% were found to be colonized by fungi, with an incidence of 80.1% in deeper burns. Commonest was *Candida albicans*. Second week was the time of maximum colonization, and same fungi were present in the oral cavity in 39 of 41 patients. This study is a pilot study and we plan to pursue the matter, this time with histopathology of biopsy specimens and repeated blood cultures for fungi to find out the incidence of invasion and relationship with morbidity and mortality.

CROSS-REPLANTATION OF RIGHT FOREARM AND HAND ON LEFT SIDE IN A CASE OF SEVERELY CRUSHED AMPUTATION OF BOTH FOREARMS, SR Tambwekar, King Fahd Specialist Hospital, Buraidah, Al-Gassim

A patient was admitted to the hospital 8 hours after crushed amputation of both forearms and hands sustained in a railway accident. He had associated head injury and few abrasions on the body. He was unconscious on arrival. Amputated limbs were preserved in the hospital at 4°C until the patient improved. Right forearm was amputated through the elbow and left forearm was amputated obliquely through mid and distal third. It was decided after a thorough debridement to perform replantation of right forearm to left side. Radius was fixed to ulna and ulna to radius, while ulnar artery was anastomosed to radial artery and radial to ulnar artery. Median and ulnar nerves were sutured to similar nerve with rotation of 180 degrees. These various anastomoses were performed successfully under the microscope. Routine postoperative treatment was given. The replant was successful. Later a prosthesis to the right side was given for total rehabilitation of the patient.

THE ART OF RHINOPLASTY DESCENDS FROM 600 BC, M Yousaf, King Fahad National Guard Hospital, Riyadh

Mastered from 600 BC by Indians and Egyptians, the modern age of corrective rhinoplasty did not start until the work of John Orland Roe in 1887. Rhinoplasty has undergone definitive changes in concept and approach since the time of Joseph, the father of the procedure. Maintenance of natural architecture with conservative and subtle techniques, as well as preserving the racial characteristics of the nose, has unquestionably helped to avoid an "operated upon" look. Three techniques were described: (1) alar flap for tip plasty, (2) correction of the crooked nose by fracturing the nasal bones at three places, and (3) augmentation rhinoplasty. These were illustrated with the methods of plaster application. Intraoperative demonstrations were shown and postoperative results provided.

SYMPOSIUM ON TOTAL JOINT REPLACEMENT

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THROMBOEMBOLISM AFTER TOTAL JOINT REPLACEMENTS, SI Al-Azzawi, Security Forces Hospital, Riyadh

Patients undergoing elective or emergency hip or knee surgery have great potential to develop deep venous thrombosis (stasis, vessel injury, hypercoagulable state). Advanced age, cardiac failure, malignant disease, and previous DVT are extra risk factors. Diagnostic methods available include impedance plethysmography, radioactive fibrinogen scanning, and venography. When pulmonary embolus is suspected, ventilation/perfusion scan and pulmonary angiography are the diagnostic procedures. Primary prophylaxis with adjusted warfarin/heparin and pneumatic intermittent compression are effective in hip and knee surgery, respectively. Combined intravenous dextran with pneumatic intermittent compression proved to be highly successful in elective hip surgery. Availability, ease of administration, and cost-effectiveness are factors that will sway the choice of individual orthopedists.

DEFORMATION OF THE TIBIAL COMPONENT CEMENT MANTLE FOLLOWING TOTAL KNEE ARTHROPLASTY, RB Bourne, AD Chris, JB Finlay, CH Roraback, University of Western Ontario, London, Ontario, Canada

An in vitro model has been developed to measure deformation of the cement mantle, sandwiched between the tibial compartment and underlying cancellous bone following total knee arthroplasty. Maximal cement mantle deformation occurred at the contact points between the femoral and tibial components. Deformation was significantly reduced by increasing the thickness of the high-density polyethylene and even more impressively by metal backing. Eccentric loading by as little as 5 degrees increased deformation in the loaded compartment by 26% and decreased that in the unloaded compartment by 62%. The addition of torsion to axial loading did not significantly alter principal or shear strains. Although surface-covering tibial components are advocated, perfect cortical rim support did not appear particularly important in reducing cement mantle deformation except for a minor effect with nonmetal-backed tibial components.

THE EFFICACY OF CPM MACHINES FOLLOWING TOTAL KNEE REPLACEMENT IN REDUCING DEEP VENOUS THROMBOSIS AND ENHANCING RANGE OF MOTION, RB Bourne, CH Rorabeck, A Lynch, University of Western Ontario, London, Ontario, Canada

In 150 consecutive patients undergoing total knee arthroplasty, half had routine physiotherapy and half had continuous passive motion applied to the operated lower limb and routine physiotherapy. No patient suffered a pulmonary embolus, but about 45% had thrombosis in the veins of the calf, whether passive motion was or was not administered. Radiographically, the deep vein thrombosis extended into or proximal to the popliteal vessels in five percent of each group. Sex, age, obesity, a history of hypertension or diabetes did not influence the incidence of venous thrombosis, but there was a higher incidence of venous thrombotic disease in patients undergoing total knee arthroplasty when cement was used for fixation of the components, irrespective of the use of continuous passive limb motion. Use of the CPM machine increased knee range of motion by 10 degrees at 1 week, but no difference was noted at 6 weeks or thereafter.

THE DESIGN OF A CLINICAL TRIAL TO ASSESS NEW TECHNOLOGY IN TOTAL HIP REPLACEMENT, RB Bourne, CH Rorabeck, University of Western Ontario, London, Ontario, Canada

The purpose of this paper is to describe a study to assess new health care technology. A prospective, randomized double-blinded clinical trial comparing cemented to cementless total hip arthroplasty has been ongoing at this institution by two surgeons. Patients between ages 18 and 75 with osteoarthritis of the hip have been included. Excluded were contralateral hip arthroplasty, knee-ankle involvement, follow-up availability, etc. Both patients and study nurses have been blinded to the type of implant. Outcome measures recorded preoperatively and at each follow-up visit included Harris and d'Aubigne hip ratings, time trade-off, 6-minute walk, sickness impact profile, and radiography including bone quality scores. Patient-borne expenses along with inpatient, outpatients, and government costs were recorded for economic assessment. Bilateral venograms were performed on day 6. Complications including dislocation, infection, and revision were assessed. The patients were stratified by age and for cement versus cementless. The titanium implant chosen had identical geometry for cemented and cementless application. To date, 82 patients have been randomized. Venography data has shown no difference between the two groups. Studies such as this are important to assess the economic implications of new health care technology so that the orthopedic community can better justify to health care providers the importance of new technology.

A PROSPECTIVE 2-YEAR COMPARISON OF THE HYBRID CEMENTED AND CEMENTLESS MILLER-GALANTE TOTAL KNEE REPLACEMENTS, RB Bourne, CH Rorabeck, L Nott, University of Western Ontario, London, Ontario, Canada.

This study compares the clinical results of 60 hybrid (cemented tibial and patellar, cementless femoral components) and 60 cementless Miller-Galante total knee replacements in osteoarthritic patients. At 2 years' follow-up by an independent observer, 96% of the hybrid and 88% of the cementless replacements had excellent or good Hospital for Special Surgery scores. Two cementless patellar components and one cementless tibial component required revision for symptomatic loosening. No cemented component required revision. Range of motion, activities of daily living, and alignment were similar in both groups. The patellofemoral joint was a major flaw in this otherwise excellent prosthesis. Nine percent had symptoms related to the patellofemoral joint (i.,e., subluxation), whereas 6% required reoperation (i.e, dislocation, polyethylene wear, loosening, fracture, or tendon rupture). Complete erosion through the polyethylene to the metal backing of the patellar component occurred in three patients and is a major concern for the future. The shallow patellofemoral groove lacks intrinsic stability, resulting in more patellofemoral subluxations and dislocations than found with other prostheses. Based on this analysis, the hybrid Miller-Galante total knee replacement with a cemented, non-metal-backed patellar component is favored over its cementless counterpart. Patellofemoral stability remains a problem to be addressed by the manufacturers.

MECHANISMS OF JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS, AF Masri, Security Forces Hospital, Riyadh

Despite many years of intensive investigations, the etiology of rheumatoid arthritis remains obscure. The pathogenesis of joint destruction has been ascribed to a combination of cellular interactions in the synovial tissue and the different chemical products: proteolytic enzymes, proteoglycans, oxygen radicals, as well as products of the complement kinin, clotting, fibrinolytic, and arachidonic acid pathways. The initial inflammatory process in the joint starts in the synovium which undergoes intense hyperplasia. A granulation tissue rich in blood vessels and active cellular elements develops and is called the pannus. The pannus acquires histochemical features that enable it to invade the neighboring cartilage. The cartilage matrix made of collagen and proteogylcans is subjected to immunochemical degradation, and multiple enzymes are involved including the collagenases. Once the cartilage is damaged, the subchondral bone becomes the next target. Osteoclasts at the bone-pannus interface are activated and produce mediators that cause bone demineralization and later bone destruction. Central to this destructive process is the presence of a triggering factor(s) and cellular elements capable of phagocytosis. The phagocytes interact with the immunocompetent B and T cells and release chemical mediators that propagate the inflammation into its chronic and destructive features.

HISTORICAL REVIEW OF JOINT REPLACEMENT, MI Dhebar, King Khalid University Hospital, Riyadh

The noted Viennese surgeon, Billroth, said, "Only the man who is familiar with the art and science of past is competent to aid in its progress in future." An attempt has been made to trace the historical milestones in the development of surgery, especially in orthopedic surgery, in relation to the advancement in metal and plastics technology. The past 25 years have witnessed extraordinary advances in application of implants to orthopedic surgery. Perhaps the single development since 1950 that has excited the most interest, not only among the orthopedic surgeons but within the whole medical community, has been the evolution of arthroplastic procedures.

TOTAL JOINT REPLACEMENT IN SICKLE CELL DISEASE, PG Moreau, King Faisal Specialist Hospital and Research Centre, Riyadh

Homozygous sickle disease is a well-known cause of avascular necrosis frequently involving the femoral head and femoral condyles. The young age of the patients, bilateral involvement, and increased frequency of postoperative complications make this a challenging disease for the orthopedic surgeon. Recent studies have shown 5-year failure rates of approximately 50% in dealing with this problem. The experience of King Faisal Specialist Hospital has been reviewed. The high incidence of positive bone cultures, despite negative joint cultures, was addressed. In our series, it appeared that septic necrosis as opposed to aseptic necrosis was the more common etiologic factor in this disease.

PCA TOTAL KNEE REPLACEMENT, MS Moukaied, King Khalid National Guard Hospital, Jeddah

Resection arthroplasty of the knee was reported as early as 1861 by Fergusson. Verneuil is generally credited with having performed the first interpositional arthroplasty of the knee in 1863 when he inserted a flap of joint capsule between the two resected joint surfaces to prevent them from growing together. In 1942 Smith Peterson's metallic femoral mould hemiarthroplasty was not successful. In 1950 Walldius and Shiers produced hinge arthroplasty to provide knee stability. The modern era of arthroplasty began with Gunston's design in 1971. He incorporated the low friction concept originated by Charnley for total hip arthroplasty. It consisted of steel surfaces articulating with high-density polyethylene surfaces, all components being cemented in bone by methylmethacrylate. The recent development of implant designs with induced biologic fixation by ingrowth of bone into porous surfaces holds exciting promise for improved long-term results. Osteoarthritis of the knee is a common problem in Saudi Arabia. Unfortunately, most of the patients referred are at a late stage, and they cannot be treated by a simple osteotomy. In September 1985 we started using PCA total knee replacement. Up to now 25 cases have been done, and the results are encouraging although long-term follow-up is needed.

A PILOT PROGRAM FOR PREDEPOSIT AUTOLOGOUS TRANSFUSION IN TOTAL JOINT REPLACEMENT, K Pang, JE Beecham, King Fahad National Guard Hospital, Riyadh

The recent increase in public concern about transfusion-transmitted infectious disease has caused rapid growth in Western countries in the use of intraoperative transfusion of autologous blood. In order to study the logistics of predeposit autologous donation in Saudi Arabia, a pilot program was established at the King Fahad National Guard Hospital. Surgeons wishing to use autologous transfusions from predeposit donations during subsequent surgery for their patients were asked to fill out request forms at patient clinic visits. Based on guidelines of the American Association of Blood Banks, an evaluation of the patient by the blood bank physician regarding suitability for donation was carried out, and a schedule of weekly single-unit donations arranged as appropriate. Notification was made to the surgeon at the completion of the scheduled donations. A discussion of the advantages and problems encountered with this approach was presented as well as comments about the suitability of such a program for Saudi Arabia.

LIMB SALVAGE PROCEDURES, RJ Rooney, King Faisal Specialist Hospital and Research Centre, Riyadh

The increase in the limb salvage procedures in the treatment of bone tumors has led to the use of prosthetic replacements. The purpose of this presentation was to discuss the indications, diagnostic techniques, surgical staging, and the utilization of prosthetic replacement in the treatment of bone tumors of the extremities.

OPTIMIZING CEMENTED TOTAL HIP FIXATION IN 1988, H Tchelebi, Security Forces Hospital, Riyadh

This subject was chosen to emphasize the current status of fixation of hip joint replacement which appears to be at a crossroads. Orthopedic surgeons currently favor cementless replacements, based on the long-term failure of cemented prostheses. Clearly, the results of cemented total hip replacements, done using the early techniques, and early designs of total hip replacements, while extremely satisfactory over the short and intermediate term, are quite unsatisfactory in the long term. This has led researchers and experts in this field to find ways to improve the long-term behavior of cemented total hip replacements. Major improvements in the results of cemented total hip replacements have already occurred secondary to the substantial improvement in cementing techniques, implant design, and increasing the fatigue life of bone cement by reducing its porosity. Major efforts have been made to improve the durability of the cemented composite, and these efforts have proved to be successful, as shown by assessment of the results at 6 years as compared to the results using the early techniques and design. Specifically, major reduction in femoral component loosening has been achieved by plugging the femoral canal, using cement gum and improving the stem. Additional improvement such as pressurization of the cement, porosity reduction, and precoating over a rough surface and metal-locked acetabular component further enhanced the durability of cemented total hip replacements.

CLOUTIER UNCONSTRAINED TOTAL KNEE REPLACEMENT AT THE SECURITY FORCES HOSPITAL: A 5-YEAR FOLLOW-UP, H Tchelebi, H Mufti, Security Forces Hospital, Riyadh

A nonconstrained total knee prosthesis designed in 1979 at St. Luc Hospital in Montreal, Canada, has been used at the Security Forces Hospital since 1983. The geometry of its femoral component simulates the normal anatomy, and the flat articular surfaces of its tibial component allow unconstrained rotation, rolling, and sliding motion as dictated by the retained cruciate ligaments. The result achieved in 21 consecutive arthroplasties (in 19 patients) was elevated after a minimum follow-up of 1 year and a maximum of 5 years. Using the knee-rating system of the Hospital for Special Surgery, 91% of the knees had excellent or good results. In 19 knees, the preoperative pain was adequately relieved and the limb was in physiological valgus alignment. Nineteen knees had normal medial-lateral stability, and two remain unstable. The average postoperative arc of flexion was 102.8 degrees. Seventeen patients could ascend and descend stairs normally. One knee had a supracondylar fracture and ended up with an arthrodesis, and one patient had a deep venous thrombosis with no aseptic loosening to date. Based on the findings in this study, in nearly 95% of knees for which total arthroplasty is indicated, a nonconstrained cruciate preserving prosthesis can provide adequate relief of pain, satisfactory axial alignment of the limb, and stability. Nearly normal kinematics of the knee can be preserved, function of the knee can be improved, and shear stress at the component-cement-bone interface can be minimized when such a prosthesis is used.

CEMENTLESS TOTAL KNEE ARTHROPLASTY, JP Waddell, University of Toronto, Toronto, Ontario, Canada

Based on the preliminary success of cementless total hip replacement, cementless total knee arthroplasty has been advocated by some as equivalent to or superior to cemented total knee replacement. A number of prosthetic systems with differing types of fixation have been advocated for this purpose. Reports in the literature have suggested that cementless fixation of the femoral component is generally successful, whereas fixation of the tibial component may continue to pose problems. Sixty-six Tricon-M uncemented total knee prostheses have been followed between 2 and 4 years after insertion. The average follow-up was 38 months. There were 40 females and 30 males with an average age of 67 years within the group. Osteoarthritis was the most common diagnosis, followed by rheumatoid arthritis and osteonecrosis. All knees were assessed using the Hospital for Special Surgery knee rating system with an average HSS score at final follow-up of 90.5 points with a mean flexion achieved of 104 degrees. Forty-eight patients were rated as excellent and seven as good. Five patients were unsatisfactory, two because of sepsis, two because of patellar dislocation, and one because of tibial component loosening requiring revision. Despite the low rate of symptomatic loosening, radiologic assessment revealed tibial lucent lines of greater than 2 mm in the three patients and subsidence of greater than 1 mm in seven patients. Tibial component loosening in uncemented knee arthroplasty appeared to be related to osteoporosis (a low Singh index being seen in many cases) undersizing of the tibial component such that it did not have contact with the cortex of the tibia peripherally, and failure to correct the varus knee to neutral or valgus. It was felt that noncemented knee arthroplasty was successful in terms of fixation of the femoral component. The tibial component remains questionable, particularly in those patients with osteoporosis and in patients in whom peripheral cortical contact with the tibial component is not achieved. The degree of tibial subsidence is directly related to the bone quality and to implant undersizing, and therefore the use of bone cement on the tibial side at least should be considered frequently in all cases of proposed cementless total knee replacement.

RATIONALE FOR NONCEMENTED TOTAL HIP REPLACEMENT, JP Waddell, University of Toronto, Toronto, Ontario, Canada

A wave of enthusiasm, unsubstantiated by long-term clinical results, has developed throughout the world for noncemented total joint replacement. In particular, noncemented total hip replacement appears to be the operation of choice for most surgeons for patients under the age of 65. The rationale for the use of noncemented total hip replacement is dependent upon our knowledge of (1) the relative ease with which certain prostheses can be incorporated into bone; (2) the known deleterious effects of the presence of bone cement on eventual prosthetic loosening; (3) demonstrable unacceptable results for cemented joint replacement on long-term follow-ups of young active patients; (4) the failure or resurfacing arthroplasty to offer a viable alternative to cemented stemmed total joint replacement; and (5) increasing patient demand for functional arthroplasty as an alternative to arthrodesis or osteotomy. Experimental evidence primarily in dogs has demonstrated the rapid incorporation of porous coated or beaded total hip components is not only possible, but perhaps preferable in certain circumstances. A clear demonstration of the problems associated with these components in experimental animals has not yet been forthcoming. Similarly, the ideal metallurgical features of these components is as yet unknown and questions remain to be answered about the porous coating: What type of coating? How should it be applied? What percentage of the prosthetic surface should be covered? A significant design alteration has been necessary to enhance the anatomic fit of noncemented components. The long-term effect of these design changes on prosthetic strength, stress-shielding of the host bone, and ease of insertion and extraction of the prostheses remains unproved. Current concepts with regard to prosthetic design, prosthetic surface treatment, metallurgy, methods of fixation, and preliminary clinical results were explored.

HISTOLOGICAL AND BASIC SCIENCE FEATURES OF CEMENTED HIP REPLACEMENT, JP Waddell, University of Toronto, Toronto, Ontario, Canada

Cemented total hip replacement remains the "gold standard" against which all other hip arthroplasty operations must be compared. Despite the current enthusiasm for noncemented joint replacement, the use of bone cement to anchor prosthetic components remains the option selected by the majority of orthopedic surgeons, particularly for patients over the age of 65. Polymethylmethacrylate is a polymer plastic with considerable strength in compression and an ability in its liquid or semiliquid form to fill cracks and crevices and provide a uniform bearing surface for prosthetic components. Concerns with regard to the use of bone cement are generally seen (1) at the time of its initial insertion into the bone and (2) many years after implantation. Research has demonstrated that profound hypotension, anoxia, bradycardia, and sudden death which have been associated with the use of bone cement at the time of cement or prosthetic insertion in fact are not related to the monomer of the cement. Research done in animals has demonstrated unequivocally that this syndrome is related to the increased intramedullary pressure generated by the insertion of the prosthesis with subsequent microemboli to the pulmonary circulation. Experimental evidence for this has been explored in detail. Late changes in the cement mantle are felt to be a combination of physiologic degradation of the bone cement with the passage of time, repetitive loading in tension (particularly on the lateral side of the femoral stem), and the production of a giant-cell-laden membrane between the cement and the bone, this membrane being excited by methylmethacrylate debris. Newer cementing techniques and improved prosthetic design have been promoted as a way of dealing with the repetitive loading factors which appear to predispose to cement failure and prosthetic loosening. Histologic evidence has been provided which suggests that the membrane characteristically associated with prosthetic loosening can develop in the absence of methylmethacrylate and in fact may be excited solely by polyethylene debris in some cases.

RANGE OF MOTION AFTER Y/S TOTAL KNEE REPLACEMENT: COMPARISON OF FACTORS BETWEEN FULL-FLEXION KNEES AND NON-FULL-FLEXION KNEES, S. Yoshino, Nippon Medical School, Tokyo, Japan.

Although total knee replacement generally has good results, the range of motion still needs to be improved. Until December 1983, we had used the Yoshino total knee prosthesis, a monocentric type. Although this prosthesis is not hinged, its stability was as good as that of the hinged type. Mobility, however, was no greater than 87 degrees. Therefore, we developed the Y/S total knee system with the aim of at least 90 degree flexion after operation. This system has several features. One is the use of a calibrated distractor in both the 90 degree flexion and full extension for objective tensioning and alignment, so that soft tissue release can be performed correctly. A second is modification of the flat posterior surface of the fibular component to allow posterior rolling back of the femur. Thus far, the average arc of motion after Y/S knee replacement has been about 120 degrees, including full flexion of knees. To know what factors are important for better postoperative motion with the Y/S total knee system, we compared various factors between non-full-flexion knees and full-flexion knees in 227 joints of 152 rheumatoid arthritis patients who underwent Y/S total knee replacement. The average duration of follow-up was 2.7 years. Comparison of the full-flexion knees and non-full-flexion knees in this series did not detect any difference except in the preoperative arc of motion, the postoperative reconstitution of the suprapatellar pouches, and the anterior distance. It has been said that the postoperative flexion degree will depend on the patient's preoperative flexion degree. This theory is correct. Postoperative suprapatellar pouch reconstitution was necessary for stretching the quadriceps fully in flexion. Good reconstitution of the patellar pouches and greater anterior drawer distance were suggested to be important factors for achieving a better range of motion after total knee replacement, the same as the preoperative movement. In addition, these factors were obtained by better operative technique and an extensive postoperative range of motion.

PRELIMINARY RESULTS OF THE ST. MICHAEL'S HIP SYSTEM IN 400 PATIENTS, JP Waddell, University of Toronto, Toronto, Ontario, Canada

A Canada-wide clinical trial of the St. Michael's total hip system is currently under way. Four hundred patients are currently enrolled in this trial with follow-up ranging from 3 months to 2 years. The results of treatment to date have been encouraging. No problems related directly to the prosthesis have been encountered, and there have been no cases of loosening of the prosthesis in any of the patients reviewed. Postoperative dislocation rate with the posterior approach remains at 3%, and there has been only one significant infection. The structure of this clinical trial, the evaluation methods used for assessment of the patients on sequential visits, radiographic parameters used to evaluate prosthetic fixation, and anticipated problems were presented in detail. Entry-controlled clinical trials for new medical devices are still uncommon. The problems associated with the establishment of such a trial, the collection and analysis of data, interpretation of results, and interaction between designer and manufacturer were explored.

MULTIPLE REPLACEMENT OF WEIGHT-BEARING JOINTS IN RHEUMATOID ARTHRITIS PATIENTS, S Yoshino, Nippon Medical School, Tokyo, Japan

By June 1983, multiple replacements (over two joints) of weight-bearing joints were performed in 51 rheumatoid arthritis patients. Three joints were replaced in 23 patients, four joints in 25 patients, five joints in one patient, and six joints in two patients. By the time of follow-up, 10 of the patients had died due to unrelated causes. Evaluation of the walking ability in the remaining 41 patients revealed that 18 of 20 previously nonambulatory patients had become able to walk indoors and outdoors. Twenty patients who were able to walk only indoors became able to walk outdoors, and one patient who had been able to walk outdoors for less than 30 minutes at a time became able to walk outdoors for longer times. Major complications occurred in 11 patients, such as femoral neck fractures in three, supracondylar fracture of the femur in three, cervical myelopathy in two, and loosening of the femoral prosthesis in two patients. The factors responsible for the poor results in two patients were cervical problems and loss of motivation.

HIP SCORING SYSTEMS: A NECESSARY EVIL, JP Waddell, University of Toronto, Toronto, Ontario, Canada

The scoring systems for evaluating the efficacy of hip operations have been available for many years. Unfortunately, they are used primarily in a retrospective sense to evaluate large groups of patients at some predetermined end-point in treatment. This is usually for the purposes of publication or presentation of data. Hip scoring systems in fact should be used on a regular basis in clinical practice by all surgeons involved in arthroplasty. All hip scoring systems have three common features: the assessment of pain, measurement of the range of motion, and functional assessment. The combination of these three features within the scoring system and the relative weighting given to each of these three components is what makes the scoring systems that are used somewhat different. The individual surgeon should have a form in his office on which he can quickly score hip or knee patients at each visit. This should be an integral part of the history and physical examination of the patient. Once the patient has been scored on the initial visit, subsequent visits can be scored using the same system, and the patient's progress or decline can be charted in this way in a relatively objective fashion. For example, if conservative treatment is adopted, the patient is seen again in 3 to 6 months, and a repeat score is done. It can be determined whether or not the patient has deteriorated in any significant way as compared to the previous visit. In a similar fashion, patients who have undergone total joint replacement and have reached an acceptable level postoperatively on the scoring system should be scored on subsequent visits, since a deterioration in the arthroplasty may be more readily evident on the basis of conscientious scoring system than on x-ray.

Announcements

The *Annals of Saudi of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publicity, notices of postgraduate courses, meetings, and lectures must be received at least 6 months before the date of occurrence. Please send relevant information to the *Annals of Saudi Medicine*, Publications Office, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

King Saud University Hospitals Postgraduate Training Programs

King Saud University Hospitals (King Khalid University Hospital/King Abdul Aziz University Hospital) are pleased to invite applications for the following postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, pediatrics, surgery, and obstetrics/gynecology.
2. Diploma courses in medical radiodiagnosis, laryngology/otology, psychiatry, and family practice.
3. Master's degree courses in pathology and family practice.
4. Residency training program in ophthalmology (in conjunction with King Khaled Eye Specialist Hospital).

For further information, contact the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P. O. Box 2925, Riyadh 11461, Saudi Arabia.

18th International Epilepsy Congress

The 18th International Epilepsy Congress is scheduled for 18-22 October 1989 in New Delhi, India. The scientific program will include presentations on primary health care and epilepsy, epilepsy and surgery, prognosis in epilepsy, and new developments in antiepileptic drug treatment. Special sessions will include a patient forum, an evaluation of the classification of epilepsies and epileptic syndromes, and discussion of epilepsy, genetics, pregnancy, and the child. For additional information, contact Professor M. C. Maheshwari, Secretary General (18th IEC 1989), Department of Neurology, Neuro-Sciences Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India.

King Faisal Specialist Hospital and Research Centre Postgraduate Training Programs

King Faisal Specialist Hospital and Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, obstetrics/gynecology, pediatrics, and surgery.
2. Five-year pathology residency training program, affiliated with the Royal College of Pathologists of Australasia and the King Saud University.
3. Fellowships in cardiology (adult and pediatric), endocrinology, gastroenterology, infectious diseases, nephrology, and oncology (adult and pediatric).

For further information contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a 5-year joint fellowship training program in pathology. The training will be at King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Armed Forces Hospital, and is a full-time program. Application is open to interested and suitably qualified residents from all over the Kingdom. To be eligible, applicants will meet the following criteria:

1. Doctors who hold MB,BS from King Saud University or equivalent degree with at least Good grade.
2. Doctors who have finished their internship in a recognized hospital with at least a Very Good grade.
3. Successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the whole period of training.

Applications and inquiries should be sent to the Director, Postgraduate Medical Education, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

IX Biennial International Congress of Cardiology

The Pakistan Cardiac Society has announced the IX Biennial International Congress of Cardiology to be held in Lahore, Pakistan, 7-10 December 1989. The official language of the program is English. For additional information, contact the Organizing Secretary, Congress Secretariat, Department of Cardiology, Mayo Hospital, Lahore, Pakistan; telephone (042) 310130, extension 13; telex 44516 HINON PK; telefax 92-42-871715.

Strategies for Health Care of the Elderly in Saudi Arabia: An International Symposium

This symposium will be held at the Northwest Armed Forces Hospital, Tabuk, Kingdom of Saudi Arabia, on 23-25 October, 1989G (24-26 Rabi Al-Awal 1410H).

With tremendous advancement occurring in every aspect of health care in Saudi Arabia, life expectancy continues to improve. Over the next decade, the elderly population will rise substantially and constitute a major faction requiring health care in the Kingdom.

This symposium, the first of its kind in Saudi Arabia, will cover the full spectrum of health care in the elderly and topics will include:

1. Common medical emergencies in the elderly
2. Problems particularly relevant in older age groups--stroke, incontinence, dementia, and parkinsonism
3. Drug prescribing in the elderly
4. Slow-stream rehabilitation and long-term care
5. Geriatric day hospital
6. Role of physical, occupational, and speech therapists

Highly distinguished speakers from the U.K., U.S., and Saudi Arabia will participate in this unique symposium. For further details, please contact either: H.W. Anderson, MD, Chief of Professional Services, Chairman, Symposium Organising Committee; or S. Kar Purkayastha, MD, Consultant Physician, Chairman Medical Education Committee, at: the Northwest Armed Forces Hospital, P.O. Box 100, Tabuk, Saudi Arabia. Tel: 966 (04) 423-5016; fax: 966 (04) 423-2795 GAMA SVC. Ltd; tlx: 681043 WKRTBK SJ.

Radiopharmaceuticals from King Faisal Specialist Hospital and Research Centre

King Faisal Specialist Hospital and Research Centre produces various radiopharmaceuticals at its Radionuclide and Cyclotron Operations facility with the aid of model CS-30 Cyclotron. These radiopharmaceuticals are produced according to international standards of good manufacturing practice. The Research Centre meets all the international standards of quality assurance and environmental safety with regard to radiopharmaceuticals.

Radiopharmaceuticals currently produced and available for distribution throughout the Kingdom and to adjoining Arab states are as follows: thallous (T1-201) chloride injection ($T^{1/2}$ = 73 h); gallium (Ga-67) citrate injection ($T^{1/2}$ = 78.3 h); iodine-123 capsules ($T^{1/2}$ = 13.1 h); iodine-123 oral solution ($T^{1/2}$ = 13.1 h); iodine-123 orthoiodohippurate solution ($T^{1/2}$ = 13.1 h); rubidium (Rb-81) → krypton (Kr-81 m) generator ($T^{1/2}$ = 4.58 h → 13 s); indium (In-111) chloride injection ($T^{1/2}$ = 2.83 d); and iodine-124 solution ($T^{1/2}$ = 4.17 d).

Currently under development are indium (In-111) oxine for cell labeling; indium (In-111) DTPA for cisternography; I-123-labeled mIBG for imaging adrenergic tumors; and I-123-labeled fatty acids for evaluation of myocardial fatty acid metabolism. Suggestions from the medical community for additional radiopharmaceuticals are welcome.

Inquiries concerning the availability, price schedule, and technical information on specific radiopharmaceuticals should be directed to Abbass H. Al-Marzouky, MD, Executive Director, Research Centre, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 2900; telex 401050 ROSPEC SJ; telefax 464-7272, extension 1049.

King Faisal Specialist Hospital and Research Centre Symposia for 1410

King Faisal Specialist Hospital and Research Centre has scheduled the following postgraduate education symposia:

1. Health Care Manpower Symposium, 3-4 October 1989 (4-5 Rabi Al-Awal 1410).
2. Fourth Annual Radiology Symposium, 10-11 October 1989 (11-12 Rabi Al-Awal 1410).
3. Symposium on Preventive and Restorative Dentistry, 17-18 October 1989 (18-19 Rabi Al-Awal 1410).
4. Annual Pathology Symposium, 31 October-1 November 1989 (2-3 Rabi Al-Thani 1410).
5. Pharmacy Practice in Saudi Arabia: Current and Future Trends, 13-15 November 1989 (15-17 Rabi Al-Thani 1410).
6. Annual Neonatology Symposium, 28-29 November 1989 (30 Rabi Al-Thani-1 Jumada Al-Awal 1410).
7. Fine-Needle Biopsy Tutorial, 5-7 December 1989 (7-9 Jumada Al-Awal 1410).
8. Symposium on Malignancies in Childhood, 6-7 February 1990 (11-12 Rajab 1410).
9. Third Annual Symposium on Excellence in Nursing, 26-28 February 1990 (1-3 Shaban 1410).
10. Symposium on Nonsurgical Management of Low Back Pain, 10-11 March 1990 (13-14 Shaban 1410).

For additional information, please contact the Director, Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; telephone (01) 464-7272, extension 1837.

Joint Board for Postgraduate Medical Education Symposia

The Joint Board for Postgraduate Education is pleased to announce the following symposia for 1410-1411 (1989-1990):

1. Geriatrics and Rehabilitation (location and dates to be announced).
2. Advances in Anaesthesia, King Fahad National Guard Hospital, Riyadh, 7-8 Rabi Al-Thani 1410 (5-6 November 1989).
3. Primary Health Care, Ministry of Health, 12-13 Jumada Al-Awal 1410 (10-11 December 1989).
4. 7th Annual Neurosciences, Riyadh Armed Forces Hospital, 10-11 Rajab 1410 (5-6 February 1990).
5. 5th Annual Paediatric Symposium, Security Forces Hospital, 7-8 Shaban 1410 (4-5 March 1990).
6. Recent Advances in Infectious Diseases, King Fahad National Guard Hospital, Riyadh, 25-26 Shawwal 1410 (20-21 May 1990).
7. Advances in Obstetrics & Gynaecology, Riyadh Armed Forces Hospital, 4-5 Rabi Al-Awal 1411 (23-24 September 1990).
8. Advances in Diagnostic Radiology, King Faisal Specialist Hospital and Research Centre, 11-12 Rabi Al-Awal 1411 (30 September-1 October 1990).
9. Advances in Thrombosis, King Faisal Specialist Hospital and Research Centre, 15-16 Jumada Al-Awal 1411 (2-3 December 1990).
10. 8th Annual Neurosciences, Riyadh Central Hospital, 27-28 Jumada Al-Thani 1411 (13-14 January 1991).
11. 6th Annual Paediatric Symposium, College of Medicine and King Khalid University Hospital, 26-27 Rajab 1411 (10-11 February 1991).
12. Gastroenterology and Hepatology, Security Forces Hospital, 10-11 Shaban 1411 (24-25 February 1991).
13. Postgraduate and Continuing Medical Education, College of Medicine and King Khalid University Hospital, 21-22 Shawwal 1411 (5-6 May 1991).

For further information, contact the Joint Board Office, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia; telephone (01) 467-1556 or 1564; telefax 481-1853; telex 403748 DARAYAH SJ.

Riyadh Armed Forces Hospital Symposia

The Armed Forces Hospital of Riyadh has announced the following calendar of upcoming symposia:

1. International Symposium on Advanced Medicine II, 17-19 September 1989.
2. Advances in Neurology and Neurosurgery, 1-2 October 1989.
3. Medical and Surgical Aspects of Hepatobiliary Disease, 19-20 November 1989.
4. Symposium on Atherosclerosis, 26-27 November 1989.
5. Modern Trends in the Management of Valvular Heart Diseases, 14-17 January 1990.

For additional information, contact the Department of Medical Studies, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia; telephone (01) 477-7714, extensions 2269, 3548, 3549, 3550; telex 401645 RKHPA SJ; telefax 477-9168.

Middle East 89

The Second Middle East Medicare Conference and Exhibition will be held from 23 to 26 October 1989 (24 to 27 Rabi Al-Awal 1410) at the College of Medicine and Medical Sciences, Arabian Gulf University, Bahrain. The Scientific Programme will include such topics as Dentistry, Geriatric and Community Medicine, Nuclear Medicine, Obstetrics and Gynaecology, and Head and Neck Surgery. For further information, contact: Mr. Mohd Sultan Al-Romaihi, Administration, Salmaniya Medical Centre, P.O.Box 12, Bahrain; tel: 279501-279502.

Annual Pathology Symposium King Faisal Specialist Hospital and Research Centre

The Annual Pathology Symposium at King Faisal Specialist Hospital and Research Centre will be on "Pathogenesis of Infections in the Compromised Host," and will be held on Tuesday and Wednesday, 31 October to 1 November, 1989 (2-3 Rabi Al-Thani 1410). Topics will include: the making of a compromised host; endocrine dysfunction and microbial disease; normal flora in health and in nosocomial infections; infection in blood transfusion recipients and drug abusers; neoplastic disease and microbial infections; histopathology of infected lung in the compromised host; histopathology of infected brain in the compromised host; infections in bone marrow transplant recipients; yeast infections; bacterial and nontuberculous mycobacterial infections in compromised patients; *Chlamydia* and virus infections in compromised hosts; monoclonal antibodies in the laboratory diagnosis of infections; antibodies and microbial pathogenesis in the compromised host; and patient management and antimicrobial therapy. A number of internationally known speakers from abroad as well as prominent pathologists from the Kingdom of Saudi Arabia will be participating. For further details, please contact: The Office of Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Telephone: Riyadh 966.1.464-7272, ext. 1837.

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Title Page. The title page must contain (1) title of the article, (2) correct names of each author plus highest academic degree for each, (3) each author's official academic and/or clinical title and affiliation, (4) name and address of the institution(s), (5) name and address of author to whom correspondence should be sent, if it differs from the first author, and (6) any disclaimers. For case reports, it is recommended that the number of authors be limited to four. Acknowledgment of support should be included in the Acknowledgment section at the end of the article.

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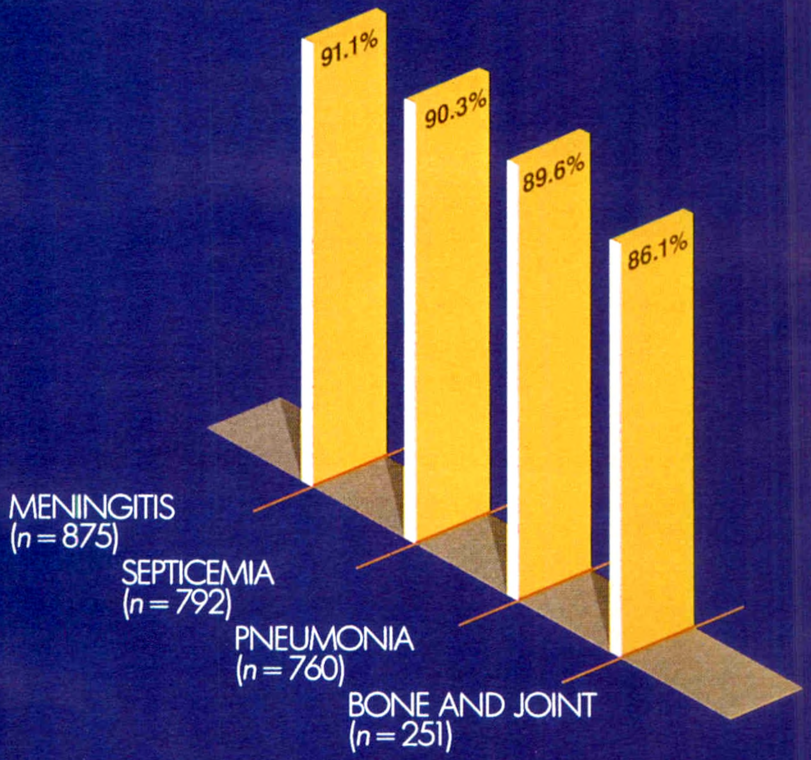

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ANNALS OF SAUDI MEDICINE

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